Archives of Internal Medicine

VOLUME 56 AUGUST 1935 NUMBER 2

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART I

O. BRENNER, M.D., M.R.C.P.

Physician for Outpatients and Physician in Charge of the Cardiographic Department, Queen's Hospital

BIRMINGHAM, ENGLAND

CONTENTS

Anatomic considerations

Normal histology of the pulmonary vessels
- Stem of the pulmonary artery
- Large branches
- Small muscular branches
- Arterioles and venules
- Capillaries
- Veins

Pathologic physiology
- Action of drugs: epinephrine, acetylcholine, histamine, pituitary extract and digitalis
- Emphysema
- Fibrosis of the lungs
- Pleural adhesions
- Heart failure
- Other functions of the lungs

Diseases of the pulmonary vessels
- Historical introduction

Scheme of present investigation
- Classification of diseases of the pulmonary vessels

Secondary pulmonary vascular sclerosis
- Classification of the conditions
- Incidence
- Gross appearances
  - Dilatation
  - Atherosclerosis
  - Distribution of sclerosis

In this series of five papers the superior numbers refer to the bibliography which will be published in connection with the last article. The superior letters refer to footnotes.

This work was done in the Cardiac Department and Pathological Laboratories of the Massachusetts General Hospital, during the tenure of a Rockefeller Foundation medical fellowship.

Microscopic changes
Grading of lesions
Stem of the pulmonary artery
Large elastic arteries
Small muscular arteries
Arterioles and venules
Capillaries
Small veins
Large intrapulmonary veins
Main extrapulmonary pulmonary veins
Muscularity of veins
Systemic vessels
Distribution of sclerosis
Changes in the heart
Etiology of secondary sclerosis
Symptoms
Primary pulmonary vascular sclerosis
Incidence
Gross appearances
Microscopic changes
Symptoms
Diagnosis
Pathogenesis
Nature of vascular changes
Relationship to right ventricular hypertrophy
Symptoms
Endarteritis obliterans
Hyperplasia of the intimal elastic tissue
Intimal endothelial proliferation
Hypertrophy of the media
Fibrosis of the media
Syphilis of the pulmonary arteries
Incidence
Morbid anatomy
Microscopic changes
Symptoms
Diagnosis
Treatment
"Ayerza's disease"
Morbid anatomy
Microscopic changes
Symptoms
Comment
Tuberculosis of the pulmonary vessels
Large elastic arteries
Small muscular arteries
Small veins
Large veins

- Rheumatism of the pulmonary arteries
  - Large arteries
  - Medium-sized arteries
  - Small arteries
  - Capillaries and venules
- Septic inflammation of the pulmonary vessels
  - Spread from infective endocarditis of pulmonary valve
  - Invasion from without
    - Arteries
    - Veins
  - Invasion through the vasa vasorum
  - Infection from the lumen
    - From an infected embolus
    - Direct intimal implantation without embolism
- Periarteritis nodosa
- New growth
  - Primary
  - Secondary
    - Tumor embolism
    - Invasion from without
      - Large arteries
      - Small arteries
      - Arterioles and venules
      - Capillaries
      - Small veins
      - Large veins
  - Influence of neoplasm on occurrence of pulmonary arteriosclerosis
- Thrombosis of pulmonary vessels
  - Incidence
  - Stem of pulmonary artery
    - Symptoms
  - Main right and left arteries
    - Symptoms
  - Large intrapulmonary arteries
    - Symptoms
  - Small muscular arteries
  - Arterioles and venules
  - Small veins
  - Etiology
- Aneurysms of the pulmonary artery
  - Traumatic
  - Mycotic
  - Congenital
  - Syphilitic
- Dissecting aneurysms
- Conclusions

The pulmonary circulation is a most vital portion of the circulatory system since through this restricted field must pass all the blood available for the left heart to pump to the various organs of the body, and only there can the essential gaseous interchanges between blood and air occur.

Moreover, the strain of disease of the heart is usually felt first in the pulmonary circuit, and the earliest symptoms of heart failure are referable to it. Yet less is known of the pulmonary circulation than of almost any other part of the circulatory system. The blood pressure in the various parts of the pulmonary circuit, its variation in health and disease and the influence of the vasomotor nerves and drugs in modifying the blood pressure and blood flow, all are practically unknown in man, and even in animals the evidence is fragmentary and often conflicting. This is largely because of the peculiar difficulties even of animal experimentation, since many of the experiments which have been devised so alter the normal conditions which they are intended to elucidate that conclusions drawn from the results are untrustworthy. Comparatively little is known even of pathologico-anatomic changes in the pulmonary circulation in disease, though such knowledge is much easier to obtain, and it is probably a necessary preliminary to the proper understanding of the pathologic physiology of the pulmonary circulation. It was these considerations which prompted the undertaking of the work reported here.

ANATOMIC CONSIDERATIONS

It is frequently said that the circumference of the pulmonary artery in the child is from 1 to 2 mm. greater than that of the aorta, while in the adult it is from 1 to 5 mm. less.[136] Jores [138] said that the aorta becomes wider than the pulmonary artery at the age of 40 in the male and at the age of 50 in the female. Others [a] have said that even in the adult the pulmonary artery is wider than the aorta. In the series of 100 consecutive autopsies which were investigated for the purposes of this paper, it was possible to find only 15 adults between the ages of 20 and 55 in whom there was no marked macroscopic evidence of sclerosis either in the stem of the pulmonary artery or in the arch of the aorta and in whom none of the factors which are usually thought capable of causing pulmonary arteriosclerosis (except systemic hypertension in 3 cases) was present. Of these 15 patients, there were only 2 in whom the pulmonary artery, 2 cm. above the cusps, was narrower than the aorta at a corresponding level. The statements to the contrary are perhaps due to the fact that cases of aortic atheroma, in which the aorta is frequently dilated, were not excluded.

Parkinson [225] stated that in males the normal circumference of the pulmonary artery is from 7.2 to 9.1 cm., and that of the aorta, from 7 to 8.1 cm., while in females the circumference of the pulmonary artery is from 6.6 to 8.9 cm. and that of the aorta is from 6.4 to 7.6 cm. Crouzon [66] said that the average circumference of the pulmonary artery is 11 cm. and that of the aorta, 8.5 cm. Clarke [57] gave from 8.5 to 9 cm. and from 7.7 to 8 cm. as the general circumferences of the pulmonary artery and aorta, respectively.

(*a*) 57, 66, 225.

Of the 15 patients in the present series there were 6 males, in whom the circumference of the pulmonary artery varied from 7.2 to 8.3 cm. (average, 7.7 cm.), while that of the aorta was from 5.6 to 8.5 cm. (average, 6.6 cm.). In the 9 females the circumference of the pulmonary artery ranged from 5.8 to 9.3 cm. (average, 7 cm.) and that of the aorta, from 5.2 to 7.3 cm (average, 6.3 cm). Though these figures were derived from data too scanty for statistical analysis, it may be stated with confidence that 11 cm., as given by Crouzon for the average circumference of the pulmonary artery, is much too high. In the present series this figure was approached only in cases of obvious marked dilatation of the pulmonary artery, usually associated with sclerosis. In only 1 case (that of a woman of 44) of the 15 cases in which there was no gross pathologic change in the stem of the pulmonary artery or any of the etiologic factors which might cause dilatation of the pulmonary artery did the circumference of the stem of the pulmonary artery exceed 8.3 cm., and in that case it was 9.3 cm. It is clear, then, that normally the stem of the pulmonary artery is a much more capacious vessel than the aorta, its diameter ranging from 85 to 136 per cent (average, 120 per cent) of that of the aorta in the male and from 97 to 136 per cent (average, 116 per cent) in the female.

The right pulmonary artery at the hilus of the lung usually has a slightly greater circumference than the left, and the sum of the circumferences of the two arteries is greater than that of the stem in any individual case. In the 15 normal persons already mentioned the circumference at the hilus ranged from 3.9 to 5.5 cm. (average, 4.5 cm.) in the males and from 3.8 to 4.8 cm. (average, 4.4 cm.) in the females.

Within the lungs[62] a branch of the pulmonary artery follows each of the larger subdivisions of the bronchi, but in the remote subdivisions the arteries divide more frequently than the bronchi[214] and finally end in small vessels lying between the alveoli and partly enclosing their mouths. The capillaries given off by these vessels run over the surface of the alveoli and then join to form venous radicles, which unite to form lobular veins at the proximal ends of the bronchioles. The pulmonary veins, unlike those in the systemic circulation, are less capacious than the corresponding arteries instead of more so. In the present series, when four pulmonary veins entered the left auricle, their circumference ranged from 2.1 to 3.7 cm. in the males and from 1.5 to 3.7 cm. in the females. If the pulmonary veins had been merged into one vessel with a cross-sectional area equal to that of the four pulmonary veins in each case, the circumference of this vessel would have been from 6 to 6.7 cm. (average, 6.3 cm.) in the males and from 4.1 to 7 cm. (average, 5.8 cm.) in the females. The circumference of such a vein would have ranged from 69 to 93 per cent (average, 78 per cent) of the circumference of the stem of the pulmonary artery in the corresponding case. The effect of this relative narrowness of the pulmonary veins is increased by the

fact that they carry not only the blood which enters the lungs through the pulmonary artery but also some of that which enters through the bronchial arteries. Probably the narrowness of the veins contributes to the ease with which "back pressure" and pulmonary congestion are caused in heart disease.

The bronchial arteries arise usually from one of the upper intercostal arteries or directly from the upper part of the descending thoracic aorta. They run with the bronchi and form capillary plexuses in the submucosa as far as the respiratory bronchioles and alveolar ducts. These join venus plexuses in the bronchial walls. Radicles from this plexus in the upper two or three divisions of the bronchi unite to form the bronchial veins, which open into the azygos and intercostal veins and the venae comites of the internal mammary vein [29] and ultimately into the superior vena cava. But the radicles from this plexus in the finer divisions of the bronchi join the pulmonary veins, and the blood is returned to the left auricle. There is some dispute as to whether there is any direct anastomosis between bronchial and pulmonary arteries, though most observers are agreed that there is not, and Berry, Brailsford and Daly [29] were unable to demonstrate in the dog a direct communication between either arteries or veins. Functioning capillary anastomoses, however, undoubtedly exist,[31] since in isolated perfused lungs a rise in pressure in the bronchial artery causes an increase in flow from both the azygos and the pulmonary vein, while a rise in pressure in either the azygos or the pulmonary vein causes a rise in pressure in both the bronchial and the pulmonary artery. This communication explains the frequency of the development of marked congestion of the bronchi in cases of heart failure at a time when there is little peripheral systemic venous stasis and possibly accounts in part for the hemoptysis which is so common in cases of heart failure. The chief communication between the pulmonary and the bronchial vascular system is by means of the capillaries, the distribution of which overlaps. Thus, the bronchial capillaries supply not only the bronchioles but also the alveolar ducts and even the interalveolar septums, while the pulmonary capillaries supply the aveoli, atria and alveolar ducts and even the respiratory bronchioles. The nutrition of the alveoli beyond the alveolar ducts is chiefly maintained by the pulmonary capillaries, while in the case of the air sacs in the walls of the alveolar ducts and respiratory bronchioles the bronchial capillaries serve a respiratory function. This overlapping is of considerable importance. Thus, ligation of the pulmonary artery or, in man, pulmonary embolism in the absence of infection or heart failure does not cause pulmonary infarction. Again, ligation of the bronchial vessels to one lobe produces no change, but ligation of both pulmonary and bronchial arteries to one lobe causes gangrene of the lung.

Probably the respiratory function of the bronchial circulation is normally of little importance, but it has been suggested that it may assume

a great deal of importance in cases of disease. In Harrison's case [129] of congenital pulmonary stenosis with a patent interventricular septum the bronchial arteries were greatly dilated, and it was possible that much of the blood aerated in the lungs was carried by the bronchial arteries. Mallory and Means [200] in their case of thrombosis of the right pulmonary artery observed greatly enlarged bronchial arteries running to the right lung. Schlaepfer [268] found that three months after the ligation of a pulmonary artery in the dog the diameter of the bronchial arteries to the corresponding lung may be increased fourfold. In such cases, however, as in the cases of Hart [130] and Stadelmann,[282] in which either the stem or both main branches of the pulmonary artery were almost or entirely occluded by thrombi and in which the authors assumed, without demonstrating, an increased circulation through the bronchial arteries, it is probable that the increased bronchial circulation maintains the nutrition of the lung and prevents infarction, but it is not likely that the bronchial arteries serve any important respiratory function. In such cases only blood which has already passed through the lungs and is therefore already oxygenated flows through the bronchial arteries, and it can undergo little if any further oxygenation in the lungs. It seems that the respiratory function of the bronchial arteries can be of importance only in cases, such as Harrison's, in which a congenital abnormality allows blood from the right side of the heart to enter the left side without first passing through the lungs, so that the blood which flows through the bronchial arteries is partly unoxygenated.

Communications between the pulmonary and the systemic veins other than the bronchial have also been described. Schlaepfer [267] showed that after experimental obstruction of the pulmonary veins, if pleural adhesions were present, veins from the surface of the lung ran out along the adhesions to communicate with tributaries of the superior vena cava, thus somewhat relieving the pressure in the pulmonary circulation by shunting some of the blood into the systemic circulation. Some clinical importance has been attached to such anastomoses. Trunicek [299] described dilatation of the veins over the front of the chest and abdomen as a characteristic sign of increase in pressure in the pulmonary circulation and stated that if these communications are well marked, emphysema may exist without hypertrophy of the right ventricle. (This seems an inadequate explanation of the frequent absence of right ventricular hypertrophy in cases of emphysema, since any obstruction to the pulmonary circulation is presumably in the pulmonary capillaries, and the pressure in the pulmonary veins might be expected to be even less than normal.) Achard [2] and Rogers [254] also mentioned dilatation of the veins over the chest in some of their cases, and in one of the cases in the present series the dilatation was so marked as to lead to an erroneous diagnosis of pressure on the superior vena cava.

NORMAL HISTOLOGY OF THE PULMONARY VESSELS

The pulmonary artery is inserted into the musculature of the right ventricle by a short tube of fibrous tissue which is continuous with the arterial tube and which is called by Gross and Kugel [121] the "annulus" (fig. 1). This consists usually of dense, almost acellular collagenous tissue which stains deep pink with Van Gieson's stain. The fibers usually run longitudinally, though occasionally they are irregular. Often, for 1 mm. or more above the attachment of the cusps, the subintimal

Fig. 1.—Photomicrograph of a longitudinal section of the root of the pulmonary artery (× 5.5; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). This section shows the beginning of the pulmonary artery, the pulmonary arterial valve and the myocardium of the right ventricle. The darkly stained media of the pulmonary artery ends in a wedge, the apex of which is immediately beneath the endothelium. The more lightly staining annulus is clearly seen, and the loose fibrillar structure of its lower part, continuous with the spongiosa of the cusp of the valve, is shown.

portion of the annulus consists of loosely arranged, delicate, longitudinal fibrils, continuous with similar tissue in the cusps of the valve, called by Gross the "spongiosa" of the valve. Many of these fibrils seem to be the elongated processes of small spindle cells, and they do not give the ordinary reactions of collagen since they stain yellow with Van

Gieson's, blue with Mallory's phosphotungstic hematoxylin and red with Mallory's connective tissue stain. The length of the annulus from the point of attachment of the cusp to the beginning of the elastic tissue and muscle of the media of the pulmonary artery varies from 0 to 6 mm. The nearer the commissure of the cusps the section is taken the less is the extent of the annulus. Usually but not always the lower half or three-fourths of the annulus is backed by heart muscle. Away from the commissures the muscle and the elastic tissue of the pulmonary artery end in a wedge the downwardly directed apex of which is subintimal. The fibrous tissue of the annulus is external to the wedge until it becomes continuous with the media and with the dense inner layer of the adventitia of the pulmonary artery. In the region of the commissures of the valve the arrangement is similar, except that the apex of the wedge of medial muscle and elastic tissue is situated immediately beneath the adventitia and there it often extends down to, or sometimes below, the root of the cusp, the fibrous tissue of the annulus being continued up on its internal aspect.

In their description of the insertion of the aorta into the ventricle (and they stated that the same description, with minor exceptions, applies to the pulmonary artery) Gross and Kugel said that the elastic fibers of the intima unite into one or more layers which sweep around the "sinus pocket" and ascend as a delicate elastic layer beneath the endothelium of that aspect of the cusp directed toward the arterial wall (the "arterialis" of the valve). This description must be somewhat modified in the case of the pulmonary artery. In the normal pulmonary artery practically the only intimal elastic tissue is the internal elastic lamina. Below the apex of the medial wedge it rapidly thins and becomes delicate. Occasionally it is continued down around the root of the cusp and into its arterialis, as described by Gross for the aorta; but, more often, just below the apex of the wedge, the lamina disappears and is replaced by a single row of delicate, fairly closely packed, circularly directed elastic fibrils, which appear as a row of dots in longitudinal section. Often these disappear before the root of the cusp is reached, and there then may be no elastic tissue in the arterialis of the cusp. Sometimes the fibers continue into the cusp, where they again become continuous.

In the annulus there is no muscle, and the only elastic tissue is represented by the few delicate fibrils lying immediately beneath the endothelium. Aortic aneurysm is usually ascribed to the destruction of the medial muscle and elastic tissue and its replacement by stretchable fibrous tissue. However, this is the normal arrangement at the root of the pulmonary artery and of the aorta, even though the area involved is small and is usually backed in its lower part by heart muscle. If the usual explanation of the origin of aneurysms is correct, it is difficult to understand why small-mouthed saccular aneurysms are not normally present at the roots of the aorta and pulmonary artery.

Stem of the Pulmonary Artery Above Its Root.—In each case the stem of the pulmonary artery was studied by means of transverse sections taken from a point about 2 cm. above the cusps. It is often said [b] that the structure of the pulmonary artery differs only in minor details from that of the aorta. It is true that the general plan of the two vessels is the same, but it is easily possible to distinguish sections of them at a glance.

Intima: Jores [138] described an elaborate organization of the normal aortic intima in the adult. The deepest layer, the "elastic-muscular longitudinal layer," consists of longitudinal elastic fibers and smooth muscle cells in a collagenous ground-substance. Internal to this is the "hyperplastic layer," [301] consisting of circular elastic fibers with some muscle cells. More internally in later life there is a layer of fibrous tissue without muscle or elastic tissue. The whole forms a layer 100 microns or more thick. This characteristic appearance is sometimes missing, the intima being then represented by a thick fibrous layer with more or less elastic tissue and perhaps a few scattered muscle cells.

In the stem of the pulmonary artery (fig. 2) this appearance is not observed. In youth and early adult life the endothelium rests directly on a thick and prominent internal elastic lamina, often seen to be composed of closely packed fibrils usually circularly directed, though some are longitudinal. In later life a thin layer of fibrous tissue often intervenes between the endothelium and the internal elastic lamina, either in the whole extent of the vessel or more commonly only in patches. The normal limit of thickness of this layer was placed at 0.024 mm. by Ljungdahl [176] and at 0.03 mm. by Costa,[63] but it is difficult to set a rigid limit since the thickening passes with no sharp line of demarcation into pathologic processes. The connective tissue is dense, is often practically homogeneous and usually stains pink but sometimes brown or a dirty yellow with Van Gieson's stain. It contains a few round, oval and irregular cells and usually in parts of its extent a great deal of fine, poorly staining elastic tissue arranged parallel to the lumen. A layer corresponding to Jores' elastic-muscular longitudinal layer was described by Torhorst,[296] separated from the rest of the intima by a strong elastic lamina and distinguished from the underlying media only by the longitudinal direction of its muscular and elastic elements. Ehlers [92] and Girous [114] described a similar layer, unevenly developed, in which, however, many of the elastic and muscular elements were circular or oblique as well as longitudinal. Though the latter observers regarded the layer as part of the media and not of the intima, all three agreed that atheromatous changes in the pulmonary artery usually begin there. Others [c] were in agreement with this. Only Hornowski [136] said that

(*b*) 63, 138, 296.
(*c*) 63, 176.

the musculo-elastic longitudinal layer in the pulmonary artery was either absent or so intimately united with the media that it was impossible to separate it.

In the present series in no case was a musculo-elastic longitudinal layer found in the intima, and in most cases nothing resembling it was seen in the media either. In 16 of the 100 patients, however (all but 1, a woman of 26 with congestive heart failure and marked pulmonary

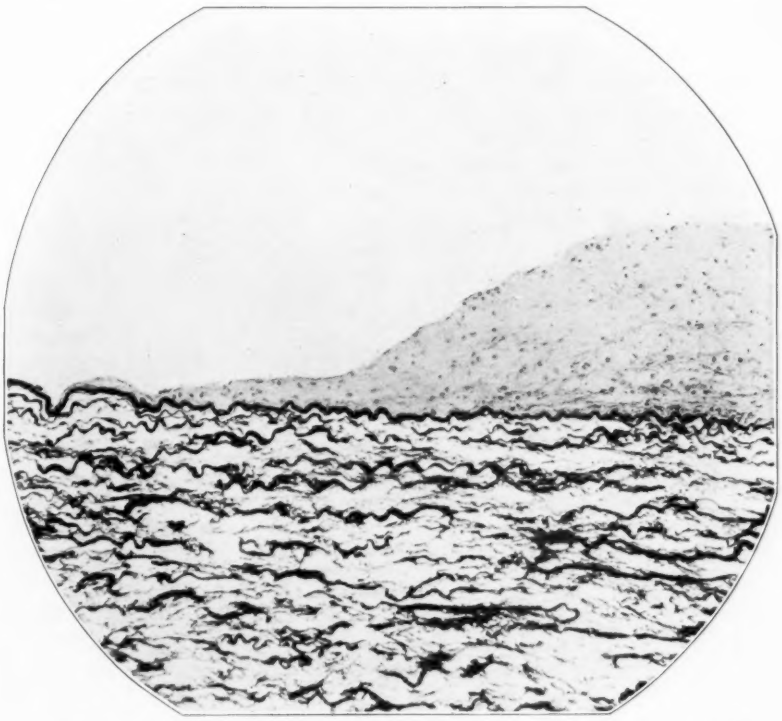

Fig. 2.—A transverse section of the stem of the pulmonary artery (× 125; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). This section shows the superficial portion of the media and intima, including a portion of an atheromatous plaque. Below the intima is normal and consists of endothelium directly on the internal elastic lamina. Above this the connective tissue gradually intervenes and develops into an arteriosclerotic patch. The media shows the normal irregularity of the elastic laminae. There is no musculo-elastic longitudinal layer.

vascular sclerosis, over 40), in some parts of the section, but never uniformly, in the superficial 0.05 to 0.07 mm. of the media the elastic membranes were thinner and more widely spaced than elsewhere, and

fine longitudinal elastic fibrils were more numerous than circular fibrils. In this region there was often much dense fibrous tissue, and the scanty muscle cells were often chiefly longitudinally arranged. Marked atheroma of the stem of the pulmonary artery was rather uncommon, but when present, it seemed to be confined to the intima and not to begin in that layer of the media. There is thus nothing in the pulmonary artery which corresponds to the three layers of the aortic intima.

The media is said to be normally from 0.8 to 1.1 mm. thick.[c] In the present series in 5 men with a normal pulmonary arterial stem and with none of the conditions usually thought capable of causing pulmonary arteriosclerosis the thickness of the media, with one exception, ranged from 0.647 to 0.797 mm. (average, 0.73 mm.). In the exceptional case the thickness was 1.462 mm. and if that case is included, the average was 0.877 mm. In a similar group of 5 normal women the thickness ranged from 0.553 to 1.115 mm. (average, 0.828 mm.). This is rather less than that found by Costa,[63] though the number of cases is too small for certain conclusions to be drawn. The general plan is similar to that of the aorta. In both, the media consists of elastic laminae, muscle and connective tissue, but these elements are somewhat differently arranged. In the aorta the elastic laminae are fairly regular in thickness and closely set. They anastomose by means of thick, oblique side-branches. Fenestrations in the laminae are small and not numerous, since each lamina can be traced for long distances without interruptions, unless its identity is lost by anastomosis with adjacent laminae. There is a great deal of muscle between adjacent laminae, mostly circularly arranged, though with some longitudinal and oblique fibers.

The structure of the pulmonary artery is much more irregular. Its elastic laminae are more scanty and more widely spaced. They are not so parallel, and they are more irregular in shape. In some places they are thin; in others they widen into irregular platelike or clublike expansions. The individual laminae appear short and can be traced only for short distances. They then end, leaving spaces filled by connective tissue, muscle and perhaps a few fine elastic fibrils. Probably this means that the fenestrations are much greater than in the aorta. Between the laminae are many fine irregular fibrils running in all directions. Some of these can be seen connecting adjacent laminae, and perhaps all would be seen to do this if they could be traced far enough. The muscle of the media is usually fairly abundant but is more irregularly arranged than in the aorta. Most of the cells are circularly, but some are longitudinally or obliquely, arranged. Occasionally alternate layers are circular and longitudinal, but usually no such regularity can be made out. Connective tissue is much more abundant than in the aorta. It occurs in large plates, parallel to the lumen, of dense, almost acellular tissue, with fine fibrils, which stain pink with Van Gieson's stain, in a

homogeneous matrix which stains a paler pink. In a large mass of fibrous tissue there may sometimes be found isolated muscle cells and short elastic fibrils. A few of the fibrous patches are often looser and more fibrillar and contain a few mononuclear cells.

Fairly large twigs from the adventitial vasa vasorum penetrate into the outermost part of the media, the various medial layers in the neighborhood being arranged concentric to the vessel. Capillaries are present in the outer half or two thirds of the media.

In old age the irregularity of the arrangement of the media is often increased and there is often an increase of the connective tissue, which is formed into large masses at the expense of the elastic tissue and muscle. It seems probable that such large masses of connective tissue have in the past been mistaken by some authors for syphilitic scars. The adventitia consists of fibrofatty tissue. Usually the layer next to the media consists of dense fibrous tissue, while the rest may be mainly fatty. There are many irregular short elastic fibers and sometimes a few small bundles of longitudinal muscle. The line of demarcation from the media is often not sharply marked. Many blood vessels and nerves are present.

Large Branches.—The structure of the branches remains essentially the same from the main right and left pulmonary arteries down to the intrapulmonary branches of about 1 mm. in outside diameter (excluding the thickness of the adventitia, which it is often difficult to demarcate from the surrounding fibrous tissue). In children the same structure is seen in arteries that are even smaller. The intima consists of endothelium lying directly on a thick internal elastic lamina. In some cases that are not otherwise abnormal a thin layer of connective tissue intervenes either in patches or over the whole circumference. This, though common, is probably pathologic. The thickness of the media varies with the size of the vessel, but it ranges from 5 to 15 per cent (average, 9.8 per cent) of the external diameter of the artery exclusive of the adventitia. This is undoubtedly too large for the arteries during life, since then the lumen would be distended. Moreover, the figures are probably not strictly comparable among themselves, since the degree of postmortem contraction probably varies. Therefore, only wide departures from the "normal" range should be accepted as pathologic. The media consists of elastic laminae which are more regular than in the stem, their number depending on the size of the artery and ranging from three or four in arteries of 1 mm. external diameter, to from sixteen to twenty in arteries 5 or 6 mm. in diameter. They are long (sometimes traceable completely around the circumference of the artery), so that fenestrations are smaller and less frequent; fairly regular in thickness, and fairly parallel, though with frequent anastomoses. Muscle is relatively more abundant than in the stem, and almost all of

it is circular, with a few longitudinal or oblique fibers. Connective tissue is much less abundant than in the stem, and in the smallest arteries of this type it is usually confined to a few small patches between the outermost two elastic laminae. In the smaller arteries the elastic laminae are finer, except the innermost and outermost, which are more prominent by contrast.

The adventitia consists of collagenous tissue of varying denseness. Often it consists of short, thick, curved collagenous fibers. There are

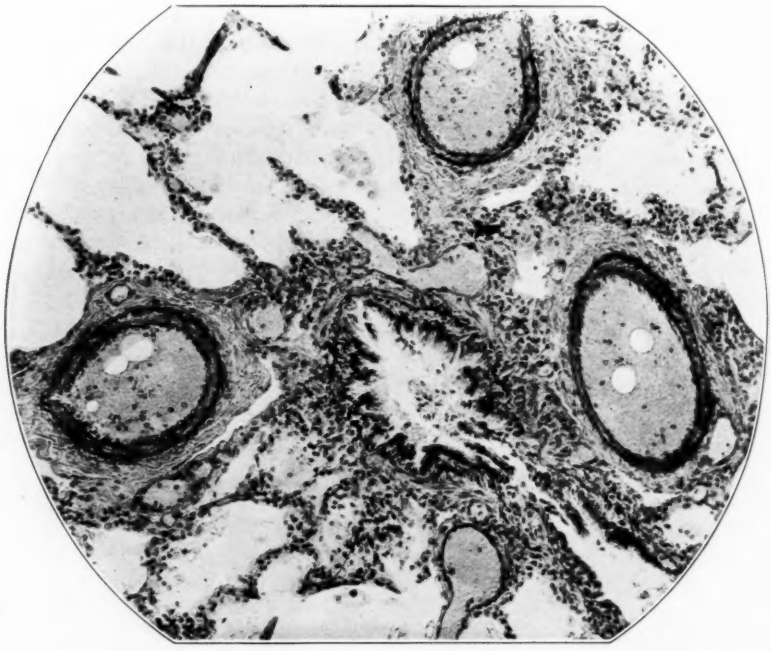

Fig. 3.—Photomicrograph showing three normal small muscular arteries grouped around a small bronchus (× 130; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The media, consisting of a thin layer of muscle between the external and internal elastic laminae, is well shown, as is also the absence of connective tissue between the internal elastic lamina and the intimal endothelium. Below the bronchus is an arteriole or venule, and above it is another. The lower one shows clearly the single fine elastic fibril surrounding the layer of endothelium.

many fine, irregular elastic fibrils, often predominantly longitudinal, and sometimes a few small bundles of longitudinal muscle. There are many blood vessels and nerves, as well as lymphatic vessels, which are well demonstrated when plugged with tumor cells.

Muscular Arteries.—The muscular arteries range in external diameter from 1 to 0.1 mm. or less and at their upper limit pass imperceptibly into the large elastic arteries. The intima consists of endothelium which rests directly on a well marked internal elastic lamina (fig. 3). The media is from 6 to 32 per cent of the external diameter (average, 14 per cent). The same remarks apply to these figures as to those for the large arteries. The media consists of circular muscle between internal and external elastic laminae. In all but the smallest arteries there are a few short, fine, irregular elastic fibrils. There is no connective tissue. The adventitia consists of a fairly thick layer of dense connective tissue.

Arterioles and Venules.—These are considered together because, owing to their similarity of structure, it is difficult to differentiate between them without seeing them joining an artery or a vein. There is no precise definition of the word arteriole, and many writers in their description of the pulmonary circulation use it as synonymous with the term small artery. In the systemic circulation it has been defined by various authorities as an arterial vessel with a diameter of less than 0.3 mm.,[197] less than 0.1 mm. or (Landis) less than 0.04 mm. Cowdry,[65] in view of these very different criteria, considered that it is not so much a question of the absolute diameter as of the relative thickness of the wall, which is greater than in any other type of vessel. It is these vessels which by the contraction and relaxation of their powerful walls regulate the blood pressure and the blood supply to the various organs. The afferent vessels of the renal glomeruli and the arterioles of the malpighian bodies in the spleen are typical examples. Measurements made in a number of cases show that these have an external diameter of from 0.023 to 0.066 mm. (average, 0.043 mm.); a lumen with a diameter of from 0.008 to 0.016 mm. or of from 18 to 50 per cent (average, 28 per cent) of the external diameter, and a muscular wall from 0.008 to 0.027 mm. thick, or from 25 to 41 per cent (average, 36 per cent) of the external diameter. Thus, after death the lumen in these vessels is about a fourth and the wall over a third of the external diameter.

There are no vessels of this type in the pulmonary circulation. The arteries down to 0.1 mm. have a media consisting of a thin layer of muscle between internal and external elastic laminae. Below 0.1 mm. (fig. 3) the wall of the vessel consists of a tube of endothelium surrounded by a single spirally wound elastic fibril, which seems to be continuous with the external elastic lamina of the parent artery. Occasionally in the larger of these arterioles the elastic fibril splits here and there to enclose single muscle cells. The walls of these vessels range in thickness from 4 to 9 per cent (average, 5.7 per cent) of the external diameter, compared with an average of 36 per cent for the systemic arterioles. Ljungdahl [176] and Trunicek [299] also described a similar structure for the pulmonary arterioles, though Trunicek called them capillaries. It is dif-

ficult to believe that vessels such as these can contract actively and so regulate the pulmonary circulation, as do the systemic arterioles for the systemic circulation; but they seem admirably fitted to follow passively the changes in the pulmonary blood pressure produced in other ways.

Capillaries.—Little need be said of the capillaries except that Krogh and Vimtrup (quoted by Cowdry [65]) stated that they have no Rouget

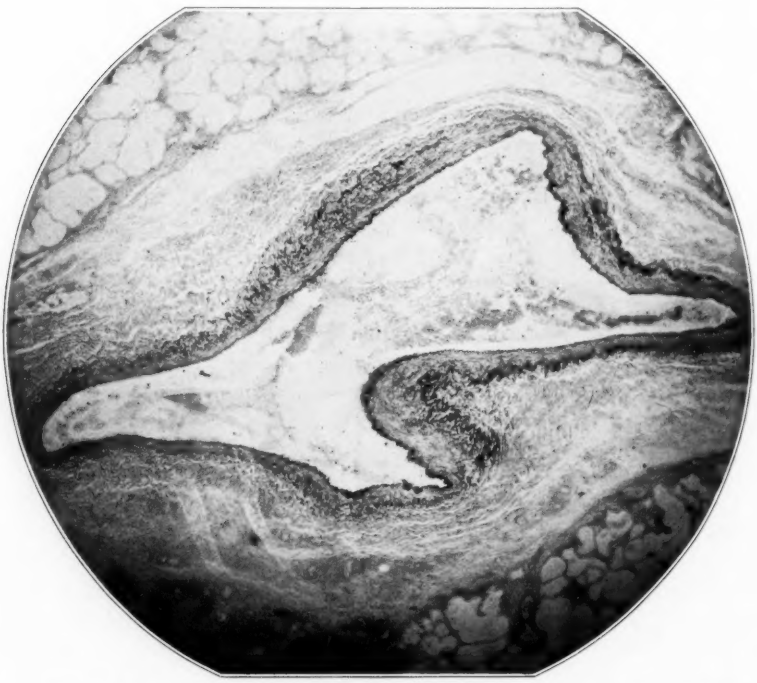

Fig. 4.—Photomicrograph of a section of a large pulmonary vein (× 21; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The intima is normal except for a patch of slight thickening over the knuckle near the middle of the lower border. The remainder of the vessel is normal. The irregularity of the elastic tissue of the media is well shown.

cells and that it is doubtful if they can contract. But since many observers now think that Rouget cells play no part in capillary contraction, their absence is not proof of an inability to contract.

Veins.—Up to a diameter of from 0.15 to 0.25 mm. the veins have the same structure as the arterioles. Above this the walls gradually thicken, though below an external diameter of 1 mm. the wall still forms

only from 2 to 7 per cent (average, 4 per cent) of the external diameter. Several rather irregular elastic fibers appear instead of one fiber, and between them there are much connective tissue and a few muscle cells. The intima still consists of endothelium directly on an elastic fiber.

In the larger veins (from 1 to 5 mm. or more in diameter) the media consists of connective tissue with many fine, irregular elastic fibers and varying amounts of irregularly arranged smooth muscle. Often there is a thin layer of muscle immediately beneath the internal elastic lamina, and bundles of muscle are scattered through the rest of the media. The adventitia is usually thick, and there is no clear line of demarcation between it and the media. It contains irregular but chiefly longitudinal elastic fibers and often bundles of longitudinal muscle. There are also many vessels here.

The main (extrapulmonary) pulmonary veins show a similar structure. The intima consists of endothelium which lies directly on an elastic lamina. The media consists of connective tissue with a great deal of fine irregular elastic tissue and a varying amount of muscle. The adventitia is a thick layer of fibrofatty tissue with many vessels and some nerves. In it a tube of cardiac muscle is continued from the left auricle for varying distances along the veins, separated from the media by a zone of fibrofatty tissue.

PATHOLOGIC PHYSIOLOGY OF THE PULMONARY CIRCULATION

There is at present no method of estimating the pressure in the pulmonary artery in man, and the methods used in animals are unsatisfactory. Scarff [266] found that the pulmonary systolic pressure in dogs was from 18 to 27 mm. and the pulse pressure was from 7 to 14 mm. of mercury. Dunn [85] found in goats that the mean right ventricular pressure for the various phases of respiration was from 9.5 to 27.5 systolic and from 1 to 11.5 diastolic. Thus the old statement that the pressure in the pulmonary artery is about one sixth of that in the aorta is confirmed for the systolic though not for the diastolic pressure. The pressure in the pulmonary veins presumably fluctuates around that in the left auricle, depending on the phases of the cardiac cycle, and the pressure in the pulmonary capillaries must be intermediate.

Other things being equal, an increased output by the right ventricle must result in an increased pressure all the way from the right ventricle to the left auricle, and Patterson and Starling [228] have shown that in the heart-lung preparation, in which, however, the conditions cannot be regarded as normal, this actually occurs. The normal stimulus to an increased output of the right ventricle is an increased venous return, such as occurs in muscular exercise. It might therefore be expected that exercise would cause an increase in the pressure in the pulmonary

artery. However, in goats [85] the mean right ventricular pressure remains unaltered during exercise, though the respiratory variations are increased, so that compensatory mechanisms come into play. One of these is that the output of the left heart is also increased, so that more blood is drawn out of the lungs, thus reducing the resistance to the flow of blood.

There is a great deal of evidence that the pulmonary vascular bed can expand and contract as required. Wearn [314] said that sometimes only one or two capillaries are open on the wall of an alveolus of the living lung, and a little later six or eight are open. Pressure on the abdominal aorta causes many new vessels to open. Schoen [272] said that many reserve capillaries at the edge of a living lung watched under the microscope open when the opposite lung is thrown out of action. When the pulmonary veins are clamped, the volume of blood in the lungs is doubled.[81] In the isolated lung perfused under negative pressure respiration an increased flow of blood leads to an increase in the volume of blood in the lungs.[70] MacGregor [189] found no microscopic change in the caliber of the vessels of the isolated cat's lung perfused at varying rates, though the rate of the flow of blood obviously changed under the influence of drugs, such as epinephrine, and sometimes the flow was actually reversed; but since the resistance to blood flow is proportional to the fourth power of the diameter, a change in diameter too small to be detected microscopically may possibly suffice to initiate great changes in the pressure and flow.

It has long been known that ligature of one pulmonary artery produces no change in the systemic blood pressure or in the output of the left ventricle,[326] and more recently Drinker [81] and Underhill [303] have shown that with the left pulmonary artery tied it is even possible to increase greatly the output of the left ventricle, the right lung freely giving passage to the requisite volume of blood. This is not possible to the same extent when the right pulmonary artery is tied, as apparently the vascular bed in the right lung is more extensive than in the left. When the left pulmonary artery is tied the total volume of the blood in the lungs is unaltered,[81] showing that the vessels in the right lung have dilated so as to accommodate the blood normally held in the left lung. Scarff [266] found that ligature of the left pulmonary artery caused a temporary rise of from 30 to 50 per cent in the pulmonary systolic pressure and of from 35 to 100 per cent in the diastolic pressure, and that the pressures returned to normal in from seven to twenty-one days. Even after from three to five months there was no appreciable increase in the size of the heart observed roentgenographically, though at postmortem examination the right ventricle was found to be slightly heavier. Holman [134] found that constriction of the stem of the pulmonary artery caused a transient fall in the systemic blood pressure and a rise in pulse

rate with gradual return to normal. The fall in the output of the left ventricle is accompanied by a systemic vasoconstriction, so that a fall of 10 mm. of mercury in the systemic pressure does not occur till the cardiac output is reduced by from 30 to 66 per cent,[112] and the cross-sectional area of the pulmonary artery must be reduced by from 61 to 86 per cent in order to produce this. Death does not follow until the cross-sectional area is reduced by from 84 to 96 per cent.

Again, in various species embolism of the pulmonary arterioles, due to the presence of multiple starch granules,[87] in amount just insufficient to cause immediate death (the animals all died in from one and one-quarter to eight hours) caused only transient changes in the right ventricular pressure; the output of the left heart was not constantly decreased and sometimes was actually increased. All these experiments show that great widening of the pulmonary vascular bed may occur by the dilatation of the vessels and the opening up of new ones, thus making possible a greatly increased flow of blood through the lungs without marked alteration in the blood pressure.

Respiration also plays an important part. In inspiration the negative intrathoracic pressure draws more blood into the right auricle. This causes an increased right ventricular output, which in the absence of compensatory factors would cause the pressure in the pulmonary artery to rise. But the reduced intrathoracic pressure causes a dilatation of the thin-walled left auricle and pulmonary veins, thus reducing the resistance to the flow of blood through the lungs. Some state that in inspiration the alveolar capillaries are lengthened and narrowed, thus increasing greatly the resistance in the pulmonary circulation. Cloetta concluded that in inspiration two opposing forces act on the alveolar capillaries: 1. A radial traction inward of the expanding alveoli which tends to dilate the vessels lying between them. When the alveoli are fully expanded, this is reversed and the capillaries are compressed. 2. A linear traction which lengthens and narrows the vessels. The net result is dilatation except at the end of inspiration, when the caliber is reduced. Daly [71] excluded the effects of the heart by artificially perfusing the isolated lungs at a constant rate under negative pressure respiration. He found that inspiration caused a fall in the pressure in the pulmonary artery. Dunn [85] in intact goats also found that the minimum right ventricular pressure, systolic and diastolic, occurred at the height of inspiration. Thus the increased right ventricular output during inspiration is more than compensated for by the increased capacity of the pulmonary vascular bed, so that the pulmonary pressure falls. Great importance has been attached to the respiratory movements as an aid to the pulmonary circulation, and it is said that if free movements are impeded by pleural adhesions, the work of the right ventricle is so increased that it must become hypertrophic.[64]

Some authors [d] have expressed the belief that the muscle of the small arteries acts as a "peripheral heart" and helps to drive the blood through the lungs. When the resistance to the pulmonary blood flow is increased the muscle of the small pulmonary arteries may hypertrophy (actually this is rare) and so take the strain off the right ventricle. They attempt in this way to explain those cases of emphysema and mitral stenosis without right ventricular hypertrophy. The evidence is flimsy, however, and in Eliaschewitz' case,[94] which was the most striking, the extra muscle in the pulmonary vessels was longitudinal, and it is difficult to see how this by its contraction could help in the propulsion of the blood.

Little is known of the effect of "back pressure" from the left auricle. The fact that the pulmonary veins are narrower than the arteries would make it easier for pressure from the left auricle to be transmitted back to the pulmonary artery. Berry and Brenner [30] in the isolated lung perfused under negative pressure respiration found that a rise in the pulmonary venous pressure caused less than the corresponding rise in the pulmonary arterial pressure and that the volume of blood in the lungs was increased. Thus, the distensibility of the pulmonary vessels prevents the transmission to the pulmonary artery of the full effect of a rise in the left auricular pressure. With the heart-lung preparation Straub found that a rise in systemic blood pressure caused an increase in the left auricular pressure and an increase in the volume of blood in the lungs, but no increase in the pulmonary arterial pressure, thus again showing the importance of the distensibility of the pulmonary vascular bed in sparing the right ventricle.

Anrep,[7] using the heart-lung preparation, found that a rise in systemic pressure does cause a rise in the pulmonary arterial pressure, but that this is due not to back pressure but to an increased coronary flow, with a resulting more rapid return to, and output by, the right heart. In the intact animal [145] the rise in pulmonary arterial pressure is minimal, as the increased return of blood by the coronary sinus is compensated for by a diminished return by the venae cavae. Berry [31] showed that sometimes a rise in systemic pressure is accompanied by a fall in pulmonary pressure, possibly owing to local reflexes. Again, if the root of the aorta is compressed [144] there is a rise in the pulmonary arterial pressure owing to the effect of back pressure, but if the abdominal aorta is compressed, the length of aorta proximal to this portion dilates to accommodate more blood, and the rise in pulmonary arterial pressure is slight. In the heart-lung preparation, if a distensible rubber bag is included in the systemic circulation,[69] a rise in systemic pressure distends the bag, the output of the ventricles diminishes and the pulmonary arterial pressure actually falls. In many cases of systemic hypertension in man the right ventricle as well as the left is hypertrophied, even in

(*d*) 64, 94, 176, 258.

the absence of heart failure, and Weiss,[320] using Stewart's formula,[289] calculated that the average volume of blood in the lungs was 24 per cent of the total volume of blood (normal, 11 to 21 per cent) and the vital capacity was decreased. This suggests that the resistance to the flow of blood through the lungs is increased.

The facts thus far mentioned show that the pulmonary circulation is largely regulated by the output of the right ventricle and the resistance in the left auricle and that the effects of these are greatly modified by the ready mechanical distensibility of the small pulmonary vessels, which prevents changes in the output and resistance from exerting their full effect on the pulmonary blood pressure. To what extent independent contraction of the pulmonary vessels in response to nervous or chemical stimuli influences the pulmonary circulation is still disputed. Many nerves accompany the pulmonary artery, though it cannot be assumed that these contain vasomotor fibers. But recent experiments seem definitely to have established the presence of vasomotor fibers to the pulmonary vessels of dogs. Daly,[73] in the isolated perfused lung of the dog with nervous connections intact, found that stimulation of the stellate ganglion caused pulmonary vasoconstriction, while stimulation of the cervical vagi caused sometimes vasoconstriction and sometimes feeble vasodilatation, but that these effects were obtained in only about half the preparations. The effects were sometimes obtained without simultaneous changes in the bronchi, showing that they were due to independent vasoconstriction and not to compression of the radicles of the pulmonary vein by contracting bronchial muscle. Hochrein and Keller [133] found that stimulation of the peripheral end of the vagus produced no change, while stimulation of the central end caused a reflex action through the sympathetic system which resulted in dilatation of the pulmonary arteries and an increase in the blood content of the lungs, but an unchanged or diminished outflow from the lungs, as a result either of a constriction of the pulmonary veins or of greater dilatation of the capillaries than of the arteries. The results are thus conflicting, but it seems probable that both constrictor and dilator fibers to the pulmonary vessels of the dog run in both the vagus and the sympathetic nerves.

ACTION OF DRUGS

Drugs produce varied effects according to dosage, species of animal, perfusion pressure, temperature and probably other factors,[72] such as the integrity of the pulmonary nerves. If the bronchial vessels are not perfused as well as the pulmonary vessels, the nerves quickly die, and this may influence the results.

Epinephrine.—Franklin,[105] in his experiments on dogs for which he used rings cut from the pulmonary vessels and suspended in Ringer's solution, found that epinephrine usually caused contraction but some-

times dilatation of the stem and extrapulmonary branches of the pulmonary artery. With the intrapulmonary arteries (the smallest used had a circumference of 4 mm.) the response was feeble and dilatation was almost as frequent as contraction. The same was true of the intrapulmonary veins, while with the large extrapulmonary veins, if there was any response, it was always contraction. Gaddum,[111] using the isolated perfused lung, showed that in the dog epinephrine causes contraction of the arteries and to a less extent of the veins, while after the administration of ergotoxine it causes dilatation of the veins and to a less extent of the arteries. This suggests that the sympathetic system supplies both constrictor and dilator fibers to both pulmonary arterioles and venules but that the supply of constrictor fibers predominates to the former and that the supply of dilator fibers predominates to the latter. In cats small doses of epinephrine cause dilatation of the venules and larger doses, constriction of the arterioles. Berry and Brenner [30] found in intact dogs that in its first circulation through the lungs (i. e., before the heart is influenced through the coronary arteries or before the vasomotor or cardioregulatory centers in the medulla are reached) a dose of epinephrine sufficient almost to double the systemic blood pressure slightly accelerates the flow of blood through the lungs, as judged by the sodium cyanide method of Weiss and Robb, suggesting that in the intact animal epinephrine, if anything, slightly dilates the pulmonary vessels. It is known that the final effect of an intravenous injection of epinephrine is to increase the pulmonary blood pressure, but this is due chiefly to the increased output of the right ventricle, possibly aided by an increased coronary blood flow and perhaps by an increased blood flow from the bronchial arteries into the pulmonary capillaries, simulating the effects of back pressure.[72] At this stage the velocity of the flow of blood through the lungs is markedly increased.

Acetylcholine.—This drug also produces varied results according to the conditions that are present. Franklin,[105] using rings cut from the isolated pulmonary vessels of the dog, found that the main extrapulmonary arteries relaxed, the intrapulmonary arteries gave no response, the intrapulmonary veins contracted more frequently than they relaxed, and the extrapulmonary veins contracted. He concluded, therefore, that since the arteries dilated and the veins contracted, acetylcholine might be expected to cause engorgement of the lungs. Gaddum and Holtz [111] found in both cats and dogs that acetylcholine in small doses caused a fall and in larger doses a rise in the pulmonary arterial pressure. With such larger doses the effect in cats is exerted on both arterioles and venules, chiefly the latter, while in dogs the main effect is on the arterioles. The changes are abolished by the use of atropine. The authors concluded that with rare exceptions the action of drugs on the pulmonary veins is in the same direction as on the arteries and that

the changes in the veins tend to neutralize those in the arteries. They therefore expressed the belief that the pulmonary veins play no important part in regulating the blood content of the lungs. This does not follow from their findings. A drug injected into the circulation will stimulate all the nerve endings that it meets for which it is specific, but it is easy to imagine that normally the nerve fibers, dilator or constrictor, to the veins may be stimulated independently of those to the arteries.

Histamine.—The results of different observers and with different species are discordant. In the dog Nixon [80] found that histamine caused a rise in pulmonary arterial and left auricular pressure probably chiefly because of the increased cardiac output, though possibly the pulmonary arterioles also contracted. This was followed by a fall in the pulmonary arterial pressure due to the constriction of the hepatic veins, the distention of the liver and the diminished return of blood to the heart. Gaddum [111] found that histamine caused contraction of both arterioles and venules. Mautner [196] found that after the intravenous injection of histamine there were a simultaneous fall in the carotid arterial pressure, a rise in the pulmonary arterial pressure, a fall in the left auricular pressure and swelling of the lungs. These changes were attributed to constriction of the pulmonary veins which imprisons blood in the lungs and diminishes the inflow to the left heart. In the cat Dixon found a rise in the pulmonary arterial pressure due entirely to dilatation of the coronary vessels and a quicker return of blood to the right heart; while Gaddum found contraction of both arterioles and venules. In the rabbit Dixon found contraction of the arterioles.

Pituitary Extract.—Holtz [135] found that in the rabbit this caused a fall in the pulmonary arterial pressure owing to the diminished coronary flow and weakening of the heart; in cats, an increased pulmonary arterial pressure owing to increased coronary flow, and in dogs, a fall in pressure owing to a diminished coronary flow. In no case was an effect of the drug on the pulmonary vessels demonstrated.

Digitalis and Strophanthin.—Eppinger [98] found in guinea-pigs' lungs perfused with Locke's solution a constriction of the pulmonary vessels when 1.2 mg. per hundred cubic centimeters of digitoxin or strophanthin was added and dilatation when the concentration was only 0.1 mg. per hundred. He suggested that in man large doses of digitalis may cause spasm of the pulmonary vessels and failure of the right heart. To support this he cited 2 cases of auricular fibrillation with mild heart failure in which the failure increased under the influence of digitalis. In these cases the concentration of the alkaloids of digitalis in the blood must have been much less than 0.1 mg. per hundred cubic centimeters, which in the guinea-pig caused dilatation, not contraction, of the pulmonary vessels, but he suggested that there may have been an idiosyncrasy of

the pulmonary vessels to digitalis, a suggestion which it is certainly difficult to disprove.

Comment.—There is thus much inconclusive evidence that the pulmonary vessels are supplied by vasoconstrictor and dilator nerves and that they react to various drugs. The reactions of both the arteries and the veins may help in regulating the total blood content of the lungs and the distribution of blood within the lungs. But the results of different investigators have been so contradictory that it is difficult to believe that this is an important factor in the regulation of the pulmonary circulation, and the effects in different species vary so greatly that it is not legitimate to transfer any of the results to man. Attempts to study the reactions of the pulmonary vessels in the isolated perfused human lung have failed because of the rapid postmortem autolytic changes, which result in the immediate onset of pulmonary edema when perfusion is begun.[30] In man the pulmonary arterioles and venules have no muscle in their walls and consist of a tube of endothelium surrounded by a single elastic fibril. It seems improbable that such vessels could control the pulmonary circulation by their active contractions, though they seem well adapted to follow passively the changes of pressure produced by other means. A slight rise of pulmonary arterial or venous pressure would distend these vessels, so that the rise in pressure would be minimized, while a fall in pressure would cause the vessels to contract passively, thus diminishing the fall. It seems probable, therefore, that the pulmonary circulation is regulated chiefly by the output of the right ventricle and the resistance in the left auricle, modified by the ready distensibility of the small pulmonary vessels, and that independent vasomotor control of the pulmonary vessels plays only a minor part.

The modifications of the physiology of the pulmonary circulation caused by disease are even less understood than the normal physiology.

EMPHYSEMA

The emphysematous chest tends to become fixed in the inspiratory position, so that respiratory movements are limited. The vital capacity is usually reduced and the residual air increased owing to atonic dilatation of the bronchi, so that in spite of the diminished ability to breathe there must be a greater respiratory minute volume to maintain normal alveolar ventilation. The reduction in the respiratory movements diminishes the aid normally given to the pulmonary circulation, throwing a greater load on the right ventricle. Corryllos[62] said that as in normal inspiration the pulmonary capillaries are dilated and that cyanosis, when present, is due to the free circulation of blood through the incompletely aerated lung. (But Blumgart and Weiss,[319] who found the vital capacity to be normal in some cases, postulated a physicochemical change in the alveolar

wall which hinders gaseous exchange.) There would thus be no reason to expect a raised pulmonary blood pressure, and this would explain the frequent absence of hypertrophy of the right ventricle. Most observers, however, believe that the pulmonary capillaries are narrowed and reduced in number. This change, if advanced enough to use up all the "reserve capillaries," would throw a great strain on the right ventricle. Blumgart [319] found that the circulation through the lungs was usually not slowed and was sometimes quickened. This shows that any obstruction in the pulmonary circulation was successfully overcome, especially as the systemic venous pressure was normal, but it does not show whether hypertrophy of the right ventricle was necessary to accomplish it.

FIBROSIS OF THE LUNGS

Fibrosis destroys many pulmonary capillaries, reduces the respiratory movements and perhaps embarrasses the heart by displacing it. Costa [64] suggested that peribronchial fibrosis may obstruct the bronchial circulation, divert the bronchial blood into the pulmonary circulation and so raise the pulmonary blood pressure. Perhaps septic absorption from tuberculous or bronchiectatic cavities may weaken the heart. Many of the alveolar walls are thickened and lined by cubical epithelium. Any blood flowing through the walls of such alveoli must remain largely unoxygenated.

PLEURAL ADHESIONS

Costa [64] and others have expressed the belief that obliteration by adhesions of both pleurae embarrasses the right ventricle by diminishing the respiratory movements and so diminishing the aid usually given by them to the flow of blood through the lungs. Dunn [86] showed that pleural effusion increases the mean pulmonary diastolic pressure in goats, and Dubrow [83] found that thoracoplasty in dogs leads to right axis deviation, as shown in the electrocardiogram.

HEART FAILURE

In the early stages of heart failure when there is dyspnea on exertion, there are no changes in the systemic arterial, capillary or venous pressure, in the cardiac output per minute, in the velocity of blood flow in the systemic vessels, in the cerebral circulation rate or in the blood chemistry.[e] The only measurable early changes are a decrease in the vital capacity of the lungs and in the linear velocity of the blood flow through the lungs, the minute volume flow still being normal. These changes are due to dilatation of the small pulmonary vessels and the opening up of new capillaries. This causes rigidity and perhaps distention of the alveoli. The total volume of the lungs may be normal or even increased

(*e*) 127, 128, 318.

(though Drinker [82] has demonstrated a diminution of the air content of the lungs after constriction of the pulmonary veins), but the residual air is increased at the expense of the reserve air. Later, pulmonary edema occurs. Modrakowski [206] showed in the isolated lung of the cat that a rise in both pulmonary arterial and pulmonary venous pressure is necessary to produce edema. The total volume of the lung is then decreased and the vital capacity still further diminished. Peabody showed that breathing remains comfortable only so long as the tidal air is less than 33 per cent of the vital capacity. The normal tidal air volume may be more than 33 per cent of a reduced vital capacity; the accessory respiratory muscles are brought into play and the patient experiences dyspnea. Harrison showed that diminution in the vital capacity causes a reflex quickening of the respiration [127] and that a rise in the venous blood pressure has the same effect.[128] Changes in the blood pressure in the aorta and in the carotid sinuses reflexly affect the rate and depth of respiration, but Heymans [132] said that changes in the pulmonary circulation have no such effect. However, Dunn [87] showed that embolism of the pulmonary arterioles causes rapid shallow respirations and that the effect is abolished by section of the vagi. This was confirmed by Moore,[210] who showed that the effect is not due to distention of the large pulmonary vessels.

In the later stages of heart failure the cardiac output lessens and the systemic venous pressure rises. Changes in the alveolar walls prevent the proper oxygenation of the arterial blood and cyanosis occurs. Deficient oxygenation of the tissues causes an accumulation of lactic acid, and these chemical changes increase the hyperpnea. In these cases failure of the right ventricle, particularly in patients with cardiac asthma, may relieve the subjective distress by diminishing the amount of blood pumped into the lungs and allowing it to accumulate in the liver and other organs.[f]

OTHER FUNCTIONS OF THE LUNGS

Aschoff expressed the opinion that the lungs act as a filter and prevent emboli from entering the systemic circulation. Such emboli may originate as thrombi in the systemic veins or they may be pieces of tumor, fat or some other substance. This is borne out by the frequency with which organized thrombi, probably embolic in origin, are found in the small pulmonary vessels (see section on thrombosis of the pulmonary vessels).

Roger [253] expressed the belief that the lungs are active in fat metabolism. After intravenous injection of olive oil in dogs, the fat globules are arrested in the small pulmonary vessels. Only a little passes into

(*f*) 56, 272, 318.

the systemic circulation. The droplets are then gradually digested by ferments attracted from the lung parenchyma. Oxygen is then necessary, and the process occurs imperfectly when the lung is congested. Roger stated that this process occurs normally in the case of the normal postprandial hyperlipemia, but since after meals the amount of fat in the systemic veins is increased, it seems that much of it is so finely divided that it passes readily through the pulmonary capillaries. MacMahon,[190] in the case of an alcoholic patient with carbon tetrachloride poisoning, found that the blood of the pulmonary artery contained enormous amounts of fat, forming a layer which was 64 per cent of the total on standing. There was no gross fat in other situations, showing that the fat released from the liver had been unable to pass through the pulmonary capillaries.

Eppinger[98] gave evidence in support of the view that the lungs destroy lactic acid and suggested that the imperfect performance of this function may be of importance in the production of dyspnea in chronic pulmonary disease.

(To be continued)

CARDIOVASCULAR COMPLICATIONS OF TRICHINOSIS

WESLEY W. SPINK, M.D.
BOSTON

In a preliminary report,[1] attention was called to the electrocardiographic changes in a severe case of trichinosis. A fatal case was also reported in which death was due to severe myocarditis and pneumonia. Larvae were recovered from the cardiac muscle by the digestion method described by Augustine and Theiler.[2] The purpose of this paper is to present the findings in the foregoing cases in more detail, to add the findings in six additional cases and to review briefly the cardiovascular complications of trichinosis.

REPORT OF CASES

The following case is one of severe trichinosis with myocardiac changes as shown in the accompanying electrocardiograms[3]:

CASE 1.—*History.*—R. K., a 38 year old Jewish housewife, entered the hospital complaining of diarrhea of two weeks' duration. Three weeks before onset she and her daughter had eaten pork chops which were thought to have been well cooked. The daughter had only a mild trichinous infection. The first symptoms presented by the patient (R. K.) were vomiting and diarrhea. There were no abdominal cramps. She had marked loss of appetite and weakness. Three days before admission puffiness of the eyelids developed. There was no edema of the lower extremities. Two days before entry she had severe generalized headache and pain in the muscles of the calves, of the shoulders and of the scapular region.

The past history was uninmportant.

Physical Examination.—The patient was well developed and well nourished, quite prostrated, with flushed features, edematous eyelids and chemosis of the conjunctivae. The tongue was coated. The chest was symmetrical, and there was a regular, sighing type of respiration at the rate of 20 per minute. The heart was not enlarged to percussion; the apical impulse was not seen or felt; there were no thrills. Auscultation at the apex revealed the sounds to be distant and muffled. There was a rapid, protodiastolic gallop rhythm. No murmurs were heard, and the pulmonic second sound was equal in loudness to the aortic second sound. The pulse was soft and regular with a rate of 120 per minute. The blood

---

From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Spink, W. W.: Clinical and Pathological Observations of the Heart in Trichinosis, J. Clin. Investigation **13**:708, 1934.

2. Augustine, D. L., and Theiler, H.: Precipitin and Skin Tests as Aids in Diagnosing Trichinosis, Parasitology **24**:60, 1932.

3. Dr. Samuel Levine called my attention to the patient.

pressure was 90 mm. mercury systolic and 60 mm. diastolic. The liver and spleen were not enlarged. Moderate pressure over the muscles of the lower parts of the legs and the deltoid muscles caused the patient to cry out because of pain.

Course and Treatment.—The daily temperature, pulse rate, respiratory rate and blood pressure during the patient's stay of forty days in the hospital are shown in figure 1.

During the first three days in the ward the patient was stuporous. The heart sounds were weak, gallop rhythm persisted and the blood pressure declined. She was able to take only fluids by mouth. On the second day the cutaneous and

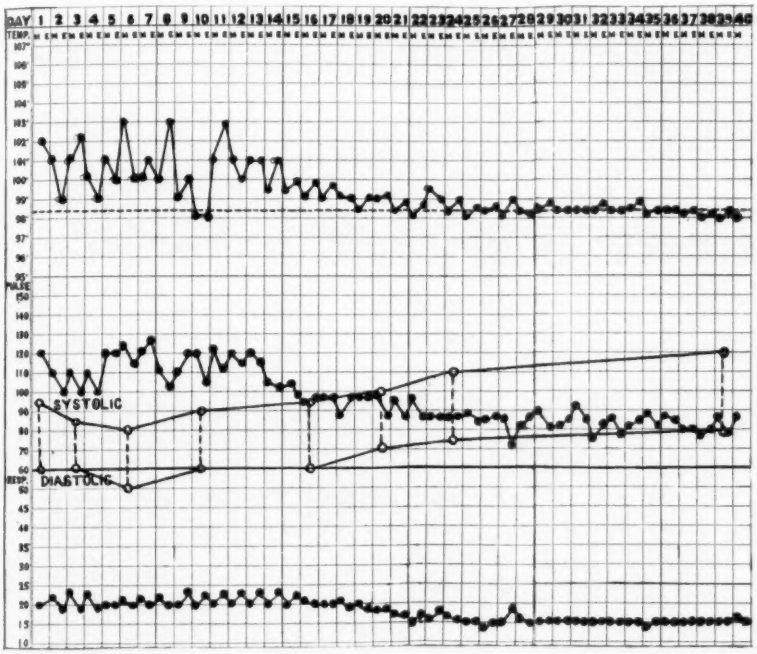

Fig. 1 (case 1).—Chart showing the daily temperature, pulse rate, respiratory rate and changes in blood pressure.

precipitin tests for trichinosis were markedly positive.[2] Because of the drop in blood pressure, the signs of a weakened myocardium and the patient's inability to take nourishment, she was given on the sixth day 300 cc. of a 10 per cent solution of dextrose intravenously and 15 units of insulin. The following day she was given 150 cc. of dextrose solution intravenously. After the second infusion the pulse rate dropped from 128 per minute to 104, the sounds at the apex were improved slightly in quality, and the rhythm was regular. The blood pressure began to rise. On the eleventh day 20 cc. of a 10 per cent solution of magnesium sulphate was administered intravenously. Two days later, or four weeks after the onset of her illness, the temperature and pulse began to decline progressively, as recorded

in figure 1. From that time until the patient was discharged from the hospital, fifty-four days after the onset, her condition gradually improved.

Electrocardiographic and Laboratory Examinations.—Three days after entry to the hospital, or on the seventeenth day of the disease, the first electrocardiogram was made. This is reproduced in figure 2. The significant finding is the inverted

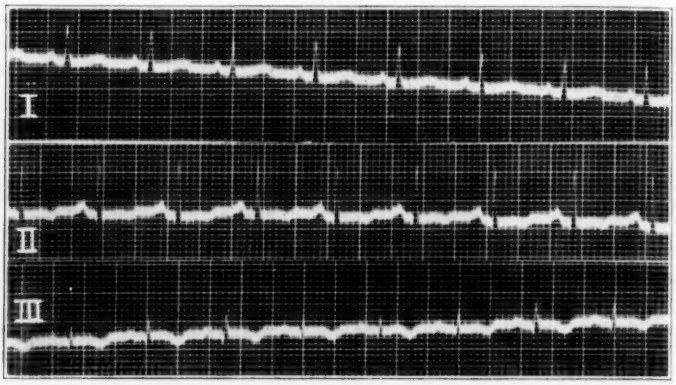

Fig. 2 (case 1).—Electrocardiogram made seventeen days after the onset of trichinosis, showing low amplitude of the T wave in lead I and inversion of the T wave in lead II.

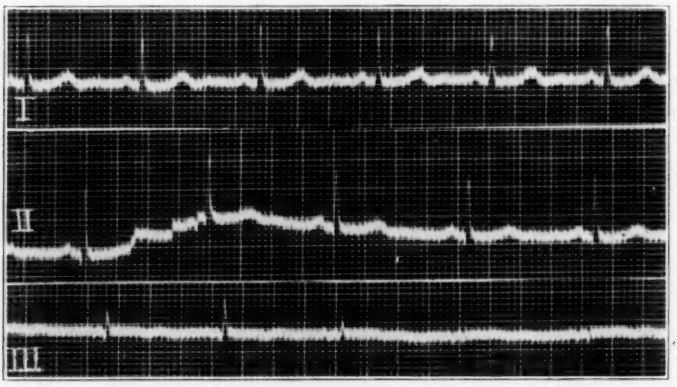

Fig. 3 (case 1).—Electrocardiogram made forty-eight days after the onset of trichinosis, showing increased amplitude of the T wave in leads I and II, with a slight increase in the height of the Q R S complex.

T wave with upward convexity in lead II which was considered by Dr. James M. Faulkner as typical of myocardiac disease. Four days later another tracing showed the same changes in the T wave. Forty-nine days after the onset of the disease a normal electrocardiogram was obtained, as shown in figure 3. During

the interval the T wave in lead II changed from inverted to upright and the voltage of the T wave in lead I and of the R wave in leads I and II increased.

Examinations of the urine and stool revealed no pertinent findings. Cultures of the blood were sterile. The nonprotein nitrogen of the blood was normal. The Kahn reaction of the blood was negative.

The erythrocytes on entry numbered 4,400,000 per cubic millimeter, and the hemoglobin content was 11.7 Gm. per hundred cubic centimeters of blood. The white blood cells numbered 10,800 per cubic millimeter, with 22 per cent polymorphonuclear eosinophils. For the first two weeks after admission the white cell count was persistently elevated, varying between 9,600 and 15,000 per cubic millimeter. The eosinophils reached a maximum of 50 per cent on the third day. Thereafter the number slowly declined until the twenty-third day when 2 per cent were present.

Subsequent Course.—The patient was seen seven months after leaving the hospital. She complained of weakness, pain in the muscles of the extremities, dyspnea and palpitation on exertion and slight edema of the ankles. Examination of the heart revealed the first apical sound slightly rough and the second sound snapping. The rate was regular. No murmurs were heard. The blood pressure was 106 mm. of mercury systolic and 70 mm. diastolic. An electrocardiogram was normal. The cutaneous test for trichinosis was positive.

The following case of trichinosis also showed electrocardiographic changes:

CASE 2.—*History.*—M. G., a 33 year old American housewife, seven days before entry ate some ham which had been cooked before purchase. The following day she was nauseated and suffered from generalized abdominal pain and diarrhea. On the third day of the illness the eyes became puffy and painful and photophobia developed. She had a severe headache and pain in the back of her neck. On the sixth day the patient complained of tenderness in the muscles of the legs, arms, shoulders and neck. For twenty-four hours before admission she experienced palpitation but no precordial pain or dyspnea. One other member of the family had mild symptoms indicative of trichinosis.

Physical Examination.—The patient was a well developed and obese woman in mild physical distress. The eyes were normal. There was tenderness on pressure over the region of the external rectus muscles but no demonstrable weakness. Tenderness was also elicited on pressure over the muscles of the neck and shoulders and of the lower part of the arms and legs. The heart and lungs appeared normal. The pulse was regular and soft, with a rate of 80 per minute. The blood pressure was 120 mm. of mercury systolic and 70 mm. diastolic.

Course and Treatment.—During the first four days in the hospital, the patient had temperature readings of from 99 to 100 F. in the evening. Thereafter there was no fever. The pulse rate for the first four days varied between 100 and 120 per minute, but fell to 80 per minute the day after fever ceased. The blood pressure remained the same throughout her stay in the hospital. The diarrhea subsided before entry, and constipation ensued. On the twelfth day of the disease the patient's reaction to an intradermal test with trichinella antigen was negative. Six days later the intradermal test was positive. On the nineteenth day of the infection, microscopic examination of a bit of tissue from the gastrocnemius muscle showed "foci of chronic inflammation; no parasites." The precipitin test of the blood serum was positive on the twenty-third day of the infection. During the third week of her illness the patient felt greatly improved, but in view of the electrocardio-

graphic changes she was kept in bed until two successive records were normal. She was discharged, free from symptoms, twenty-six days after the onset of the illness.

Three weeks after discharge her only complaint was that she tired easily. She had no muscular tenderness. An electrocardiogram at that time was normal.

Electrocardiographic and Laboratory Examinations.—Two days after entry an electrocardiogram showed slight sinus arrhythmia. The T wave in lead I was upright; that in lead II, was flat, and those in leads III and IV were inverted. The flat T wave in lead II was considered by Dr. James M. Faulkner as suggestive of myocardiac involvement. Four days later an electrocardiogram was considered normal, with the T wave of lead II upright. Another normal record was obtained two days before discharge.

The urine and stool were normal. The nonprotein nitrogen content of the blood was normal, and the Kahn reaction was negative.

The blood on admission showed 4,900,000 red cells per cubic millimeter, a hemoglobin content of 102 Gm. per hundred cubic centimeters and 18,100 white cells per cubic millimeter with 30 per cent polymorphonuclear eosinophils. The white cell count slowly fell to 9,700 per cubic millimeter with 30 per cent polymorphonuclear eosinophils on the day of discharge from the hospital, the twenty-fifth day of the disease.

The following case illustrates a severe attack of trichinosis complicated by bronchopneumonia and myocarditis, which terminated fatally:

CASE 3.—*History.*—L. T., a 38 year old married Italian laborer, entered the hospital in an incoherent state. He complained of weakness and of pain in the forehead. About eight weeks before entry he obtained some salted pork, and during the following two weeks he ate about 4 pounds (1.8 Kg.) of this meat without cooking it. About three weeks before entry the patient's wife noted that he walked as if he were lame and stiff and that he moved his arms slowly and stiffly. A few days later he complained of pain in the back. That night he went to bed because of chills and fever. A physician who was called stated that the patient had the "grip." The temperature was 102 F. From that time on he remained in bed, took little nourishment and became weaker. Two weeks before entry both eyes "became bloodshot," and a week later the face swelled markedly down to the neck. This lasted about three days and then subsided. The patient had a slight cough, productive of yellow sputum. Two days before entry and following an attack of coughing, he expectorated three mouthfuls of bright red blood. He then became disoriented, suffered from generalized itching and scratched constantly.

Physical Examination.—The patient was well developed and well nourished, disoriented mentally and moderately dyspneic. Examination of the eyes revealed hemorrhages in the lateral aspects of both sclerae, the left being about 2 mm. in diameter and the right, 7 mm. The right fundus had a small fusiform hemorrhage along one of the retinal veins. The lips were dry and cracked; the tongue was dry and coated and the pharynx injected. The heart was of normal size to percussion with a regular rate of 120 per minute. The sounds were of poor quality. However, no abnormal sounds or murmurs were audible. The blood pressure was 90 mm. of mercury systolic and 50 mm. diastolic. On percussion the lungs showed dulness to flatness posteriorly from the midscapular region to the base; tactile fremitus was absent over the same area; the breath sounds and spoken voice were diminished over the scapular region and absent at the base;

crackling râles were heard only over the right midscapular region. The abdomen was tense throughout with no palpable masses and no tenderness. The extremities were normal, but the reflexes were sluggish.

Laboratory Examination.—One blood culture was sterile. The nonprotein nitrogen content of the blood was 75 mg. per hundred cubic centimeters. There were 10,000 white cells per cubic millimeter with 90 per cent polymorphonuclear neutrophils, 5 per cent lymphocytes, 3 per cent polymorphonuclear eosinophils, 1 per cent monocytes and 1 per cent basophils. The red cells and platelets appeared normal. The precipitin test of the blood serum was positive for trichinosis.

Course.—The general condition became progressively worse. The second day after entry the patient became very toxic, cyanotic and restless. Three days after entry he had signs of marked pulmonary congestion and died.

Autopsy (Dr. Edward R. Irgens).—The postmortem examination showed trichinosis, bronchopneumonia of the lower lobes of both lungs, pulmonary edema and congestion, slight cardiac hypertrophy, slight arteriosclerosis of the coronary arteries and aorta and acute tracheobronchitis.

Microscopic examination of the heart (fig. 4) showed that the interstitial connective tissue and connective tissue around the small vessels were infiltrated by polymorphonuclear neutrophils, eosinophils and a few large mononuclear cells. There were scattered necrotic muscle fibers infiltrated by polymorphonuclear neutrophils and eosinophils. No larvae were recognized in several different sections.

After sections for microscopic examination had been taken from the heart, it was carefully washed in running water and then digested in artificial gastric juice. Dr. Donald L. Augustine examined the sediment carefully and found fourteen larvae of Trichinella spiralis. These larvae were of the more mature size usually found in skeletal muscle and not of the younger forms found in the circulating blood. This excludes the possibility that they had been present in the blood vessels of the heart.

The fourth case is one of a trichinous infection complicated by right hemiplegia:

CASE 4.—*History.*—F. M., a 42 year old married Italian woman, presented the symptoms of an infection of the upper respiratory tract. A physician diagnosed the condition as "severe influenza." For four days she was prostrated and feverish. She then showed improvement, but on the seventh day her husband found her in bed, unable to talk or use her right arm or leg. She was subsequently under the care of Dr. Nathan H. Garrick, who called my attention to the case.

Physical Examination.—The patient was a well developed and slightly obese woman with flushed features, dry and cracked lips and flaccid paralysis of the left side of the face. The pharynx was injected. The palatal reflex was not elicited. The heart sounds were rapid, regular and distant; there were no murmurs. The pulse was soft and weak, with a rate of 140 per minute. The blood pressure was 90 mm. of mercury systolic and 50 mm. diastolic. The right arm and leg showed flaccid paralysis. Knee jerks were absent. The biceps reflexes were present and equal. On the right side ankle clonus and Babinski's sign were present.

Course.—The patient's temperature, which was 101 F. at the end of the first week, declined by lysis and became normal a week later. The pulse and respiration likewise returned to normal. The patient slowly improved so that eleven weeks after the onset of the illness she was able to walk. There remained, however, right hemiplegia and paralysis of the left side of the face.

Laboratory Examination.—On the eighth day of the illness the cerebrospinal fluid was normal. The white blood cells numbered 15,500 per cubic millimeter, with 85 per cent polymorphonuclear neutrophils and no eosinophils. The erythrocyte count and hemoglobin content were normal. One week later leukocytosis was still present, but there were 12 per cent polymorphonuclear eosinophils. At the end of three weeks the percentage of eosinophils had risen to 42. The patient was thought to have trichinosis, and seven weeks after the onset the cutaneous and

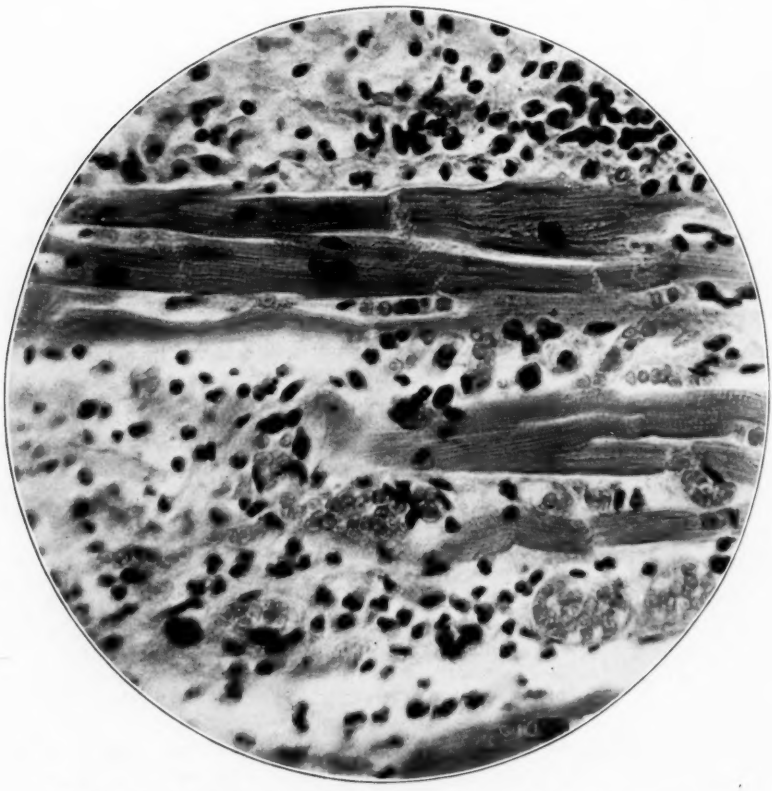

Fig. 4 (case 3).—Photomicrograph of the cardiac muscle, showing necrotic muscle fibers infiltrated by leukocytes, but no trichina larvae (× 48).

precipitin tests for trichinosis were strongly positive. An electrocardiogram made five weeks after the onset showed tachycardia and left axis deviation. Roentgen examination of the heart showed slight enlargement.

Electrocardiographic Findings in Additional Cases.—I had observed twenty-six cases of trichinosis before the patient in case 1 was seen. Because of the findings in case 1 clinical data obtained in the preceding

twenty-six cases were reviewed. As a result two more cases showing inversion of the T waves during the course of trichinosis may be added. In a third case, in which chronic rheumatic disease of the heart as well as trichinosis was present, the patient showed a temporary intraventricular block. Low amplitude of the Q R S complex during the acute stage of the infection was present in a fourth case.

COMMENT

For several years the question has been raised whether the cardiac lesion of trichinosis is due to a direct invasion of the muscle by larvae or to blood-borne toxins. Zenker [4] in 1860 first observed the larvae in the heart muscle of a patient in whom the disease had been fatal. Five years later Cohnheim [5] described the cardiac lesion in another patient as that of parenchymatous degeneration. Frothingham [6] in his description of the postmortem appearance of the myocardium stated that there are active cellular infiltration and necrosis of cardiac muscle. In one section he saw under the microscope part of a Trichina larva lying outside the vessels and muscle fibers.[7] Prym [8] found the larvae of T. spiralis in the myocardium of two patients who had died. Horlich and Bicknell [9] reported the case of a patient dying of acute myocarditis in the fifth week of the disease. Larvae were observed microscopically in the cardiac muscle. It is significant that Prym [8] found living larvae in the pericardiac fluid and that Gruber [10] described a fatal case of trichinosis complicated by recent inflammatory lesions in the pericardium.

Other observers have reported similar observations in experiments on animals. Graham,[11] working with white rats infected with T. spiralis, observed inflammatory foci in the myocardium and larvae between the muscle fibers. The largest number of larvae were noted about the ninth

4. Zenker, F. A.: Ueber die Trichinen-Krankheit des Menschen, Virchows Arch. f. path. Anat. **18**:561, 1860.

5. Cohnheim, J.: Tödliche Trichinose mit parenchymatöser Degeneration von Leber, Herz und Nieren, Virchows Arch. f. path. Anat. **33**:447, 1865.

6. Frothingham, C.: A Contribution to the Knowledge of the Lesions Caused by Trichina Spiralis in Man, J. M. Research **15**:483, 1906.

7. Dr. F. B. Mallory permitted me to examine the original section and to see the larva to which Frothingham referred.

8. Prym, P.: Ueber Trichinose beim Menschen, Centralbl. f. allg. Path. u. path. Anat. **34**:89, 1923.

9. Horlich, S. S., and Bicknell, R. E.: Trichinosis with Widespread Infestation of Many Tissues, New England J. Med. **201**:816, 1929.

10. Gruber, G. B.: Ueber die Beteiligung des Herzens und der Gefässe an der menschlichen Trichinose, Zentralbl. f. Herz- u. Gefässkr. **17**:319, 347, 359 and 381, 1925.

11. Graham, J. Y.: Beiträge zur Naturgeschichte der Trichina Spiralis, Arch. f. mikr. Anat. **50**:219, 1897.

day of the infection. After that time it became more difficult to find them. Graham's observations were confirmed by Zoller,[12] who worked with guinea-pigs. He observed that after the second week of infection larvae were rarely found in the myocardium. Zoller concluded with Graham that either the larvae were killed in situ or left the myocardium rapidly and entered the circulation again. Zoller expressed a belief that the damage to the cardiac muscle was only temporary, as he found no evidence of permanent alteration of myocardiac tissue.

From the foregoing observations, it seems that there is a definite etiologic relationship between the presence of larvae in the myocardium and myocarditis. However, as late as 1919 Simmonds [13] was unable to find the larvae in cardiac muscle, and he stated that the damage to the myocardium was due to toxic substances from the trichinae carried by the blood to the heart. It appears from the recent work of Dunlap and Weller [14] "that it is the presence of the larvae in the myocardium and their active migration and not a blood-borne toxic substance which produces the characteristic myocarditis." Their first evidence was that in a series of white rats infected with T. spiralis; myocardiac changes with the larvae present in the muscle were found as early as five days after infection and for some time thereafter. Their second evidence was that as soon as active migration of the larvae ceased myocardiac changes were not observed even though encystment of larvae in the skeletal muscle occurred to a marked degree. Myocarditis of toxic origin would not have subsided at this stage.

The histologic picture of myocarditis occurring in trichinosis is not specific. Whereas Cohnheim originally described the lesion as one of parenchymatous degeneration, subsequent investigators have shown that the process is an active, cellular infiltration, usually focal but distributed throughout the myocardium with the production of necrotic and fragmented fibers. Small hemorrhages may be present in the cardiac tissue in the earlier stages. It is to be recalled that Cohnheim's autopsy was performed on a partially decomposed cadaver. In experiments on animals myocarditis may occur as early as the fifth day of infection [14] or as late as the fifteenth day.[12] The cellular response in human cases is for the most part that of the lymphocytic series. Occasionally eosinophils predominate in the inflammatory process. Leukocytes appear to play only a slight rôle, as there are seldom more than a few present. A review of the reports of cases in which the patient died of a com-

12. Zoller, H.: Ueber die Herzmuskelentzündung im Verlauf der Trichinose, Virchows Arch. f. path. Anat. **265**:430, 1927.

13. Simmonds, M.: Ueber Myocarditis trichinosa, Centralbl. f. allg. Path. u. path. Anat. **30**:1, 1919.

14. Dunlap, G. L., and Weller, C. V.: Pathogenesis of Trichinous Myocarditis, Proc. Soc. Exper. Biol. & Med. **30**:1261, 1933.

plicating myocarditis shows that death usually occurred between the fourth and the eighth week of infection.[15]

Gruber [10] stated that the vascular system may be affected by trichinosis as follows: 1. Edema, especially of the face and eyes, may occur. 2. Congestion and hemorrhage are frequently seen in the conjunctivae and sclerae. Bloody diarrhea may result from a pronounced inflammatory hyperemia, limited chiefly to the ileum, as demonstrated by Zenker. 3. Hypotension has occurred, in which a decreased vascular tonus may persist well into convalescence. Gruber contended that this is a result of a toxic effect on the vasomotor centers and that the systolic pressure cannot be elevated by epinephrine or strychnine. However, Cheney [16] succeeded in raising the blood pressure markedly with epinephrine in a severe case of trichinosis with hypotension. 4. Thrombosis and infarction may result, as shown by Rupprecht, who found peripheral venous thromboses in twelve cases of trichinosis. Gruber presented the findings in a fatal case of trichinosis in which severe myocarditis with a fresh thrombus in the ventricle occurred.

Herrick [17] recorded a case of severe trichinosis complicated by a femoral phlebitis. Kilduffe, Barbash and Merendino [18] observed a case of trichinosis complicated by femoral thrombosis which occurred about ten days after the onset of the disease. Amputation of the extremity was necessary, and the patient died. Postmortem examination showed that the left femoral and left external iliac vessels were thrombosed up to the point of bifurcation from the common iliac vessel. No trichinae were found in the clot. Graham [11] found the embryos in sections from a rat's artery.

Gruber and Gamper [19] examined the brain of a patient who died of trichinosis. They found emboli with young larvae in them. The trichinosis was associated with acute myocarditis and thrombi on the endocardium. Another case, reported by Bloch and Hassin,[20] was that of a

15. Christeller: Fälle von Trichinose, Deutsche med. Wchnschr. **44**:869, 1918. Proskauer, cited by Strauss: Ueber Trichinose, Berl. klin. Wchnschr. **58**:121, 1921. Weller, C. V., and Shaw, M.: Myocardial Failure Due to Trichinosis, Tr. A. Am. Physicians **47**:41, 1932. Prym.[8] Zoller.[12] Simmons.[13]

16. Cheney, G.: Sporadic Trichinosis with Extreme Hypotension, J. A. M. A. **86**:1004 (April 3) 1926.

17. Herrick, W. W.: Review of Recent Studies in Trichinosis, J. A. M. A. **65**:1870 (Nov. 27) 1915.

18. Kilduffe, R. A.; Barbash, S., and Merendino, A. G.: A New Jersey Outbreak of Trichinosis with Report of a Case Complicated by Femoral Thrombosis, Am. J. M. Sc. **186**:794, 1933.

19. Gruber, G. B., and Gamper, E.: Ueber Gehirnveränderungen bei menschlicher Trichinose, Verhandl. d. deutsch. path. Gesellsch. **22**:219, 1927.

20. Bloch, L., and Hassin, G. B.: Trichinosis Complicated by Encephalitis, M. Rec. **91**:537, 1917.

young man in whom left hemiparesis developed in the eighth week of the disease and who died in a convulsive state. At autopsy there was an excessive vacuolation of brain tissue, caused principally by the enormous amount of enlarged perivascular spaces.

Master and Jaffe [21] recently reported the electrocardiographic changes in four cases of trichinosis. Taking an average number of eight records in their four cases, they found that 50 per cent showed tachycardia, 25 per cent showed a prolonged P R interval (0.22 second maximum) and 33 per cent showed inversion of the T wave.

I have observed thirty-five sporadic cases of trichinosis in the past three years. Electrocardiograms were obtained in eighteen of the cases. Abnormal electrocardiographic changes were noted in six (33.3 per cent) of these cases, the ones reported in this study. The earliest changes were observed in the second week of the disease. Only one case presented clinical evidence of myocardiac damage. The electrocardiographic evidences of myocardiac disease in trichinosis are the changes in the T wave and the low amplitude of the Q R S complex. The conducting mechanism may also be affected, as shown by the presence of intraventricular block in one of the cases. These findings demonstrate the importance of close observation for cardiac changes in severe cases of trichinosis.

The finding of larvae in digested cardiac tissue confirms the observations of other investigators that the invasion of the myocardium by the parasite appears to be closely related to myocarditis.

It is difficult to draw any definite conclusions in regard to the patient in whom right hemiplegia occurred during the course of a trichinous infection. However, since thromboses and infarctions were reported to have occurred in patients with trichinosis and since the parasite is known to have invaded the brain, there is a possibility of a direct relationship between the trichinosis and the hemiplegia.

SUMMARY

Acute myocarditis occurring in trichinosis may be a nonspecific inflammatory reaction due to the invasion of the myocardium by larvae.

A review of the literature shows that other cardiovascular manifestations include congestion and hemorrhage of the eyes, lungs and gastro-intestinal tract; edema; thrombosis; embolism with infarction, and hypotension.

Six of eighteen cases of trichinosis (33.3 per cent) showed electrocardiographic changes. These changes included an initial flattening or

21. Master, A. M., and Jaffe, H.: Electrocardiographic Evidence of Cardiac Involvement in Acute Disease, Proc. Soc. Exper. Biol. & Med. **31**:931, 1934.

inversion of the T wave, especially in lead II, the wave subsequently becoming upright; low amplitude of the Q R S complex, and intraventricular block.

The postmortem changes in a fatal case of trichinosis with myocarditis are presented. Another case is recorded in which trichinosis was complicated by a permanent right hemiplegia.

OBSTRUCTING PERICARDITIS

EFFECT OF RESECTION OF THE PERICARDIUM ON THE CIRCULATION OF A PATIENT WITH CONCRETIO CORDIS

C. SIDNEY BURWELL, M.D.
AND
D. FLICKINGER, M.D.
NASHVILLE, TENN.

The symptoms and signs of concretio cordis as a type of obstructing pericarditis were clearly described by Volhard and Schmieden [1] in 1923. They measured the venous pressure and found that it was elevated. Beck and Griswold [2] in 1930 were able to produce in dogs constricting pericardial scars associated with an elevated venous pressure, a diminished cardiac output, a small pulse and edema. Resection of these scars was followed by a fall in the venous pressure, a rise in the cardiac output and a diminution in the edema.

Burwell and Strayhorn [3] in 1932 reported quantitative studies of the circulation in a young man subsequently proved to have concretio cordis. He exhibited a high venous pressure, a small pulse pressure and a diminished cardiac output per minute and per beat. Exercise was associated with an increase in the arteriovenous oxygen difference; but no increase occurred in the output per beat. These studies seem to indicate that the essential defect in the circulatory mechanism was failure of the heart to relax to a normal extent. This patient died suddenly following a resection of the pericardium. Another patient who had previously been successfully treated by operation for a similar condition of the pericardium exhibited venous pressure, pulse pressure and cardiac output within normal limits.

In 1934 Maltby [4] reported determinations of the output of the heart in three patients with obstructing pericarditis. The cases were

From the Department of Medicine of the Vanderbilt University School of Medicine.

1. Volhard and Schmieden: Ueber Erkennung und Behandlung der Umklammerung des Herzens durch schwielige Perikarditis, Klin. Wchnschr. **2**:5 (Jan. 1) 1923.

2. Beck, C. S., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome, Arch. Surg. **21**:1064 (Dec.) 1930.

3. Burwell, C. Sidney, and Strayhorn, W. David: Concretio Cordis: I. A Clinical Study, with Observations on the Venous Pressure and Cardiac Output, Arch. Surg. **24**:106 (Jan.) 1932.

4. Maltby, Alice B.: Cardiac Output in the Pick Syndrome, Proc. Soc. Exper. Biol. & Med. **31**:853 (April) 1934.

reported in detail by Beck and Cushing.[5] In each of these patients the output of the heart was diminished as compared with normal values. In two of the cases, determinations were made also after the relief of the obstruction by operation. The output in one patient rose only slightly (from 1.79 to 2.05 liters); the output in the other patient rose significantly (from 2.11 to 2.96 liters). In each of these patients operation was followed by a reduction in the previously elevated venous pressure and by relief of symptoms.

The present report deals with the study of the circulation in a patient with concretio cordis before and after successful surgical treatment.

REPORT OF A CASE

A 17 year old Negro boy entered the Vanderbilt University Hospital on Oct. 5, 1933, complaining of swelling of the abdomen.

The illness had begun ten weeks before entry with fatigue, feverishness and lethargy which led the patient to take to his bed. On the same day he observed a vague discomfort in the epigastrium which shortly became a sharp and knifelike pain. This pain was increased by inspiration and accompanied by a feeling of breathlessness. It lasted four days and subsided gradually.

He then was permitted to get up, and he felt fairly well except for weakness. He failed to gain weight despite the fact that his appetite and digestion were good. Two weeks later (five weeks before entry) he observed a tight feeling around the abdomen; this persisted and increased. Several days later he fainted rather suddenly. He was again bedfast, and within a day or two it was observed that his abdomen was swelling and was tender to pressure. Both the swelling and the discomfort increased, and eight days before admission to the hospital ½ gallon (1.89 liters) of clear fluid was removed from his abdomen.

In the five weeks preceding admission he had several attacks of nosebleed and a little cough, productive on two occasions of a small amount of blood.

His past history revealed excellent general health and strength. He had had measles, whooping cough, chicken pox and a respiratory infection called influenza. At no time had there been symptoms referable to the cardiorespiratory system. The family history was not helpful. There was no close association with known tuberculosis.

Physical examination revealed a tall, emaciated Negro boy. He appeared moderately uncomfortable. The temperature was 99 F., the pulse rate 110 and the respiratory rate 26. The skin gave evidence of recent loss of weight.

The retinal veins were distended, even when the patient sat up. The veins of the neck were both distended and firm. The thorax was symmetrical, but expansion was diminished. At the base of each lung the percussion note was flat; vocal fremitus was absent, and the breath sounds were diminished. These changes were more extensive at the base of the right lung.

The apex impulse of the heart was neither seen nor felt. The left border of dulness was 7 cm. from the midsternal line. The heart sounds were distant, regular and rapid. No murmurs or accentuations were heard. The radial pulse was small, quick and paradoxical. The blood pressure was approximately 106 systolic and 88 diastolic during expiration and 100 systolic and 90 diastolic during inspiration.

5. Beck, C. S., and Cushing, E. H.: Circulatory Stasis of Intrapericardial Origin, J. A. M. A. **102**:1543 (May 12) 1934.

The abdomen was distended, and the signs of a large amount of ascites were present. The edge of the liver was felt 10 cm. below the right costal margin in the midclavicular line. Rectal examination revealed no hemorrhoids. The extremities showed wasting and distention of the veins but no demonstrable edema.

The urine showed a trace of albumin, a moderate number of leukocytes and a few hyaline casts. The blood contained 4,200,000 red cells and 10,900 white cells per cubic millimeter and 11 Gm. of hemoglobin per hundred cubic centimeters. The Wassermann and Kahn reactions were negative. A roentgenogram of the chest revealed only a slight enlargement of the cardiac shadow on both sides. There appeared to be fluid at the base of the right lung and thickened pleura at that of the left. Fluoroscopic examination revealed no visible pulsation of the heart and no shift with change in position of the body. The electrocardiogram showed sinus tachycardia, an inverted T wave in all leads and no shift of the electrical axis with changes in the position of the patient.

The venous pressure was 385 mm. of salt solution in the femoral vein and 350 mm. in the median basilic vein.

The patient thus exhibited the classic combination of a high degree of venous congestion with a relatively small, fixed heart. Moreover, there was no evidence of valvular disease, there was no hypertension, the pulse pressure was low and the pulse was paradoxical. A diagnosis of obstructing pericarditis was made. On the basis of experience with similar cases it was believed that tuberculosis was probably the cause of the pericarditis.

During the first week of the patient's stay in the hospital the abdomen was tapped twice, and over 6 liters of greenish-yellow hazy fluid was obtained. The fluid had a specific gravity of 0.019 and contained 500 cells per cubic millimeter. Smears and cultures revealed no bacteria, and a guinea-pig inoculated with the fluid remained well. The patient's heart rate continued to be elevated and was usually between 110 and 140. The temperature varied from 99 to 101 F. The condition remained practically unchanged for seven weeks. During this period the abdomen required tapping on four occasions, yielding a total of 20 liters of fluid. The paradoxical quality of the pulse continued.

During this time fever was present regularly in the evening, the temperature usually reaching 101 F. This fever was believed to be due to an active pericarditis. The activity of the pericardial infection was for many weeks accepted as a sufficient contraindication to operation. During this period, however, the patient gained no ground; there was, aside from the fever, little evidence of intoxication, and the severe discomforts and disabilities were based on the obstruction rather than on the inflammation in the pericardium. It was therefore decided, after this period of observation, that relief of the pericardial obstruction was necessary.

Accordingly, on Nov. 29, 1934, an operative attack on the pericardium was carried out by Dr. Alfred Blalock. A greatly thickened and inextensible pericardium was revealed, the maximum thickness of the parietal layer being 7 mm. Several encapsulated accumulations of purulent fluid were encountered, amounting to about 25 cc. in all. (Culture from this fluid gave a pure culture of Staphylococcus aureus.) The character and relations of the thickened pericardium are shown in figure 1. A large part of the anterior portion of this thickened pericardium was resected. Following this resection the pulsation of the heart increased visibly in amplitude.

The resected portions of the pericardium were composed of tough cartilaginous-feeling fibrous tissue. Microscopic examination showed fibrous tissue with diffuse leukocytic infiltration and focal collections of round cells. In certain areas there

were great numbers of polymorphonuclear leukocytes. There was no evidence of tuberculosis. With the Goodpasture stain many cocci could be seen in the granulation tissue on the cardiac side of the pericardium.

Following this operation there was an immediate improvement in the patient's condition. The liver became smaller; the veins of the neck appeared less distended, and the venous pressure was about 100 mm. lower than before operation.

Nine days after operation many of the original symptoms and signs reappeared; the liver increased in size, and fluid accumulated in the abdomen. At this time

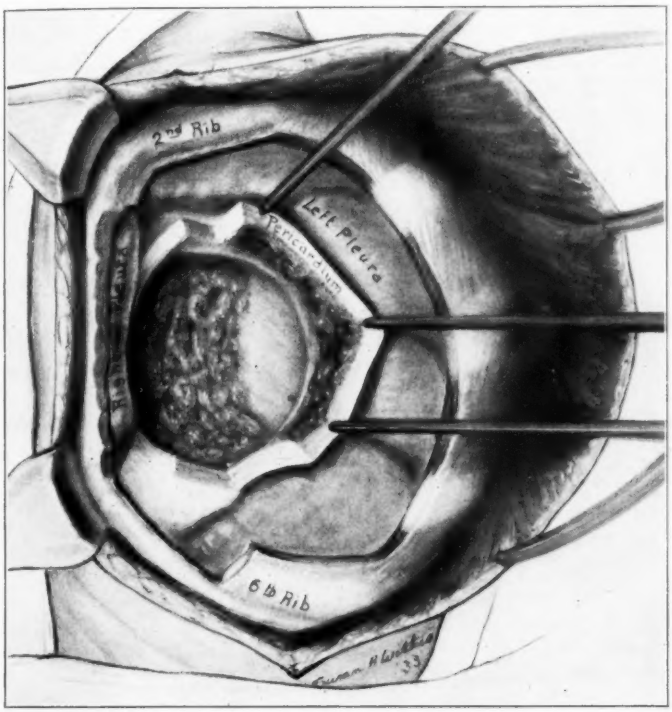

Fig. 1.—The heart and pericardium as exposed during the operation. The pleural reflections were dissected free for a greater distance than is shown in the drawing.

also there was evidence of a massive pleural effusion on the left. Some regression of the symptoms was obtained by thoracentesis with removal of a transudate. For ten days after this the patient exhibited the same signs and a venous pressure of over 300 mm. There was then a gradual change for the better, with an ultimate disappearance in the signs of congestion and a fall in the venous pressure. Five months after admission and three and a half months after the operation the patient was permitted to leave the hospital. At that time he was able to be up all day without signs or symptoms indicative of obstruction to the entry of blood into the heart. Only the final venous

pressure reading of 200 mm. of water indicated that some obstruction was still present. Fluoroscopic examination at that time revealed a cardiac pulsation of approximately normal extent.

His subsequent course was one of continual slow improvement. When last seen (July 9, 1934) he was able to sleep lying flat in bed and to walk 3 miles (4,828 meters) without undue fatigue. Signs of congestion were absent, and the venous pressure as measured on the arm was 125 mm. of saline solution.

NOTE.—On a subsequent visit (Oct. 15, 1934) he reported that he could do moderately vigorous physical work without distress. The venous pressure at this time was 118 mm.

STUDIES IN VENOUS PRESSURE

The venous pressure was studied by the direct method of Moritz and Tabora,[6] using a syringe with a side-arm as suggested by Griffith,

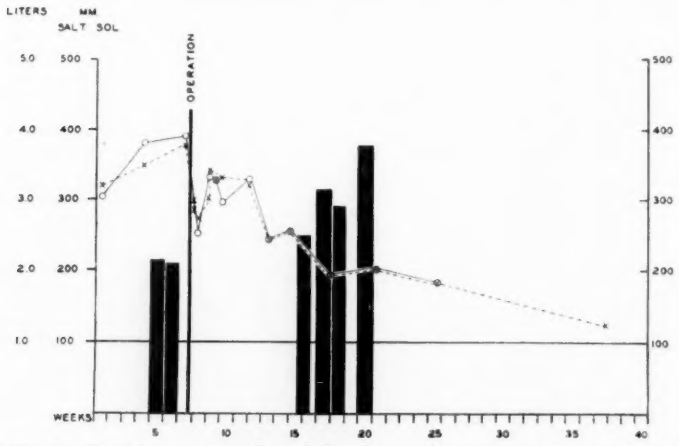

Fig. 2.—Graphic representation of the changes in venous pressure and cardiac output during the period of observation and treatment. The black columns denote the cardiac output per minute. The femoral and cubital venous pressures are designated by circles and crosses, respectively.

Chamberlain and Kitchell.[7] Observations were made frequently during the patient's stay in the hospital. Because it was considered possible that there might be a difference in the degree of obstruction of the superior and that of the inferior vena cava, measurements were made on the veins of both the arm and the leg. In general, the differences observed were slight, and it was concluded that there was no great

6. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

7. Griffith, George C.; Chamberlain, C. T., and Kitchell, J. R.: A Simplified Apparatus for Direct Venous Pressure Determination Modified from Moritz and Tabora, Am. J. M. Sc. **187**:371 (March) 1934.

difference in the degree of obstruction. Figure 2 illustrates the changes in venous pressure which took place during the period of observation and treatment. The period before operation was marked by a continuous rise in the venous pressure. Operation was followed by an immediate but transient drop in the venous pressure. The secondary rise in venous pressure was associated with the occurrence of hydrothorax and probably with a considerable reaction in the pericadium itself, with a consequent increase in the degree of obstruction. It appears that as this reaction subsided the obstruction was reduced, the venous pressure fell and the symptoms improved. When the patient was last seen, eight months after operation, the venous pressure as measured on the arm was found to be 125 mm. of water, a figure only slightly above normal.

The Output of the Heart and Related Functions Before and After Operation for Concretio Cordis

Date	Heart Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference, Cc. per Liter	Output of the Heart		Venous Pressure (Arm), Mm. of Saline Solution
				Per Minute, Liters	Per Beat, Cc.	
11/24/33	...	207	96	2.16	..	376
11/27/33	116	217	104	2.09	18	...
11/29/33	Partial resection of pericardium					
1/27/34	118	235	92	2.54	22	259
2/ 3/34	118	233	74	3.16	27	...
2/ 6/34	114	228	80	2.86	25	...
2/21/34	108	271	72	3.79	35	200
3/ 5/34	...	...	..	....	..	208
4/ 4/34	...	...	..	....	..	186
7/ 9/34	...	...	..	....	..	125

STUDIES OF THE OUTPUT OF THE HEART

Measurements were made of the output of the heart by the acetylene method of Grollman, with the three sample technic introduced by Grollman, Friedman, Clark and Harrison.[8] The results are summarized in the table.[9]

Before the operation which released the heart from the fibrous tissue which encircled it the output of the heart was about 2.1 liters per minute; the output per beat (the stroke volume) was only 20 cc.; the arteriovenous difference (the oxygen utilization) was 100 cc. per liter. The patient thus had a small output per minute, a very small output per beat and a high arteriovenous difference. The figures are comparable to those observed in similar cases by Burwell and Strayhorn and by Maltby.

After the operation four determinations of the cardiac output were made. The total output varied between 2.5 and 3.8 liters, and the

8. Grollman, Arthur; Friedman, Ben; Clark, Gurney, and Harrison, T. R.: A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**:751 (Sept.) 1933.

9. Dr. Ben Friedman and Dr. Harry Resnik Jr. made these determinations.

arteriovenous difference, between 72 and 92 cc. per liter. The last observations, made several weeks before the patient's discharge, showed a cardiac output of 3.8 liters and an arteriovenous difference of 72 cc. These figures are within the limits of normal. Even the output per beat increased and reached 35 cc.

As is shown in figure 2, the cardiac output rose as the venous pressure fell and as the patient's strength and comfort increased.

COMMENT

Such a diminution in total cardiac output as this patient exhibited may be expected to lead to weakness and fatigability. The small output per beat cannot be increased in this condition,[3] and this limitation may be expected to lead to tachycardia, a low pulse pressure and a limited tolerance for exercise. The diminution in cardiac output is thus an important factor in the production of symptoms in patients who suffer from obstructing pericarditis.

The increase in venous pressure is obviously another important factor in the production of symptoms. Aside from the changes in cardiac output a sufficient increase in venous pressure can lead to venous distention, to engorgement of the liver, to the formation of peripheral edema and to the transudation of fluid into the peritoneal and pleural cavities. In this patient changes in the size of the liver and in the rate of formation of ascites were related to changes in the venous pressure.

The importance of differentiating cases of pericardial disease with incomplete filling of the heart from cases of heart failure with incomplete emptying is obvious; therapeutic procedures which are useful in the one may be useless or injurious in the other. The differences and similarities which exist between the manifestations of the two conditions are found to depend on differences and similarities in the dynamics of the circulation in the two instances.

It has been shown that patients with concretio cordis exhibit a diminished cardiac output per minute and per beat, a fixed output per beat, a small pulse pressure and venous congestion with high venous pressure. Evidence of comparable diminution in cardiac output and in blood pressure is observed in various forms of acute circulatory collapse (including the forms associated with syncope, with hemorrhagic shock, with severe tachycardia and with coronary occlusion), but diminution of such a degree is rare in and not essential to congestive heart failure, the result of chronic cardiac disease.[10] Comparable venous congestion and comparable elevation of systemic venous pressure are

10. Friedman, Ben; Clark, Gurney; Resnik, Harry, Jr., and Harrison, T. R.: The Effect of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure, Arch. Int. Med., to be published.

seen in patients with severe chronic failure but are not seen in acute circulatory collapse except when the latter is due to cardiac tamponade, in which case there is obstruction, or to coronary occlusion, in which case there is heart failure. When occurring in chronic disease the combination of the evidence of markedly diminished cardiac output with the evidence of severe venous congestion usually indicates pericardial obstruction to the entry of blood into the heart. When, in addition, there is little or no enlargement of the heart, pulmonary congestion is slight as compared to peripheral congestion; signs of valvular disease are absent; the heart is fixed and pulsates little, and a pulsus paradoxus is present; the picture is distinctive enough for confident diagnosis.

Moreover, in concretio cordis venous congestion and venous pressure often attain degrees which are rare in so-called congestive failure. Thus in the patient under discussion the venous pressure was as high as 390 mm. of salt solution or about 30 mm. of mercury. Furthermore, like others of our patients with concretio cordis, he had a history of recurrent nosebleed during the period of his present illness, and the retinal veins were visibly distended even when he was sitting erect with the retina approximately 250 mm. above the right auricle.

But it is the combination of this high degree of congestion with the feeble pulse and diminished pulse pressure (evidences of diminished cardiac output) that points toward the diagnosis of pericarditis with obstruction.

This discussion has dealt with the alterations in circulatory dynamics associated with concretio cordis. In the main these alterations are similar to those brought about by fluid in the pericardium, which were so precisely described by Cohnheim.[11] In this instance also, especially when the fluid accumulates rapidly, the signs of congestion are observed in combination with the signs of diminished output. The conditions are to be differentiated mainly by examination of the heart, it not being forgotten that chronic pericarditis may begin with an obstructing effusion and terminate with an obstructing scar.

SUMMARY

A case is reported in which a high degree of obstructing pericarditis was present. This pericarditis was due to infection of the pericardium with Staph. aureus. Removal of a portion of the pericardium was followed by a fall in venous pressure, a rise in cardiac output and an increase in pulsation of the heart. Increased venous pressure and decreased cardiac output appear to be the chief mechanisms underlying the symptoms and signs of concretio cordis.

11. Cohnheim, Julius: Lectures on General Pathology, London, New Sydenham Society, 1889.

PULMONARY TUBERCULOSIS OF THE LOWER LOBE

DAVID REISNER, M.D.
NEW YORK

The question concerning the nature and location of the incipient changes in reinfection forms of pulmonary tuberculosis has enjoyed renewed interest in recent years. There has been considerable discussion on the subject of subapical versus apical location of the early manifestations. The importance of the infraclavicular infiltrations and their significance as precursors of manifest and progressive phthisis has been especially stressed by the German school. It is not intended here to dilate further on this point, which has been so thoroughly discussed by numerous writers. Suffice it to state that the results of these investigations definitely indicate that in a large proportion of the clinically manifest forms the earliest changes are situated outside the apex of the lung.

The interest in the subject presented in this paper was originally aroused by a group of cases in which the location of the changes is frequently considered as atypical for adult forms of pulmonary tuberculosis. Such forms, while by no means common, are nevertheless not infrequently encountered, if one has an opportunity to study a large number of patients with pulmonary tuberculosis. I refer to those instances in which the involvement is found in the midfield of the lung close to the structures of the root. Because of their apparent proximity to the hilar area on the roentgenogram, these lesions are variously referred to as hilus, perihilar or parahilar forms of pulmonary tuberculosis. From such roentgen findings the inference has frequently been drawn that there exists an anatomic relation of these forms with the structures of the root, such as extension of the pathologic process by contiguity from the tracheobronchial lymph nodes into the lung, retrograde infection by way of the lymph vessels or perforation of a caseated lymph node into the bronchial tree with subsequent involvement of the lung. It has been suggested that lesions of this character represent a pathogenetic and clinical entity which is distinct from the usual mode of involvement in the majority of adult forms of pulmonary tuberculosis, and it is thought that they exhibit certain similarities with the childhood

---

From the Department of Tuberculosis of the Metropolitan Hospital, New York, and the Sea View Hospital, Staten Island, N. Y. (Dr. George G. Ornstein, Director).

forms. Such views have been advocated by a number of authors, more recently by Alexander,[1] Bernard,[2] Bernard, Lelong and Renard[3] and Faber.[4]

However, at no time could such modes of infection as have just been outlined be reconciled with actual anatomic findings. There has been a decided opposition on the part of pathologists to accepting these views. Ghon,[5] Ghon and Kudlich,[6] Graeff and Kuepferle[7] and Tendeloo[8] have been emphatic in stressing the complete lack of evidence in favor of such conceptions. According to Graeff and Kuepferle, the apparent discrepancies between the anatomic and roentgen findings are merely the result of the superimposition of densities located in various planes of the thoracic cavity. A few clinical observers have likewise called attention to such pitfalls in the interpretation of roentgen findings, notably Brecke,[9] Fleischner[10] and Ulrici.[11]

It was therefore thought that a systematic study of such cases with an attempt at topographic localization of the lesion would be of value in clearing up this seemingly controversial question. However, as the material accumulated it became evident that the great majority of lesions presenting the roentgen appearance of the so-called hilus forms

1. Alexander, H.: Ueber Hilustuberkulose bei Erwachsenen, Beitr. z. Klin. d. Tuberk. **62**:318, 1926.

2. Bernard, L.: Le début intercléido-hilaire de la tuberculose pulmonaire, Presse méd. **38**:373 (March 15) 1930.

3. Bernard, L.; Lelong, M., and Renard, G.: La localisation péri-hilaire de la tuberculose pulmonaire chronique de l'adulte, Ann. de méd. **21**:366, 1927; Essai pathogénique sur les localisations de la tuberculose pulmonaire chronique, Ann. de méd. **21**:353, 1927.

4. Faber, K.: Perihilar Pulmonary Tuberculosis in Adults, Hospitalstid. **73**: 879 (Sept. 4) 1930; Perihilar Pulmonary Tuberculosis in Adults, Acta med. Scandinav. **75**:403, 1931.

5. Ghon, A.: Genese und Anatomie der Tuberkulose, in Ghon, A., and Jaksch-Wartenhorst, R.: Die Tuberkulose und ihre Bekaempfung, Vienna, Emil Haim & Co., 1922.

6. Ghon, A., and Kudlich, H.: Zur sogenannten Hilustuberkulose, Med. Klin. **24**:1661 (Oct. 26) 1928.

7. Graeff, S., and Kuepferle, L.: Die Lungenphthise, Berlin, Julius Springer, 1923, vol. 1.

8. Tendeloo, N. P.: Studien über die Entstehung und den Verlauf der Lungenkrankheiten, ed. 2, Munich, J. F. Bergmann, 1931; Pathologische Anatomie, in Brauer, L.; Schröder, E., and Blumenfeld, F.: Handbuch der Tuberkulose, ed. 3, Leipzig, Johann Ambrosius Barth, 1923, vol. 1.

9. Brecke, A.: Allgemeine Diagnostik, in Brauer, L.; Schröder, E., and Blumenfeld, F.: Handbuch der Tuberkulose, ed. 3, Leipzig, Johann Ambrosius Barth, 1923, vol. 1.

10. Fleischner, F.: Lobäre und interlobäre Lungenprozesse, Fortschr. a. d. Geb. d. Röntgenstrahlen **30**:181 and 441, 1923.

11. Ulrici, H.: Zur Frage der sogenannten Hilustuberkulose, Beitr. z. Klin. d. Tuberk. **46**:38, 1921.

were in reality lesions involving the superior portion of the lower lobe, especially its apical and subapical region. This resulted in focusing the attention of this study on the problem of tuberculosis of the lower lobe in general.

Involvement of the lower lobe in pulmonary tuberculosis is generally regarded as an irrelevant and, as a rule, late occurrence in the course of progressive craniocaudate phthisis. Cases in which the lesion starts in the lower lobe are looked on as extreme rarities. It seems that most pathologists and clinicians, as well as roentgenologists, concur in this view. In considering the question whether such statements are in accord with actual conditions, it is necessary to call attention to certain facts which are bound to limit their validity.

With regard to anatomic observations, it must be pointed out that patients with early lesions in which the point of origin can be established with a fair degree of probability rarely come to postmortem examination, while the end-stages of an advanced lesion seldom permit a reconstruction of the topographic and chronological sequence of events. It is probable that a lesion which begins in the lower lobe and subsequently involves the upper lobes may be devoid of any definitely distinguishing features at the autopsy table and may thus present the picture of common progressive craniocaudate phthisis. The great advantage of clinical and roentgenologic follow-up studies in establishing the location of the early lesion and its subsequent evolution is therefore apparent.

With respect to statements from clinical and roentgenologic sources which emphasize the extremely rare occurrence of tuberculosis of the lower lobe, it is important to point out that one frequently fails to make a clear distinction between lesions of the lower lobe and basal lesions, and that these designations are often used promiscuously. This appears to be chiefly due to the fact that the topographic boundaries of the lobes are often lost sight of. Lesions confined to the superior portion of the lower lobe present neither clinical nor roentgenologic features indicative of a basal process and are in many instances responsible for the somewhat vague term hilus tuberculosis.

A sharp differentiation between lesions involving the superior portion of the lower lobe and true basal involvement is of considerable significance. There is no doubt that early involvement limited to the base of the lung is an extremely rare and unusual occurrence in the reinfection forms of adult tuberculosis. This, however, does not apply to the cranial portion of the lower lobe. It is fairly well known that this area is not infrequently the site of secondary changes in relatively early stages of lesions of the upper lobe. This fact was definitely stressed as early as 1888 by Fowler,[12] who pointed out that "the upper

12. Fowler, J. K.: Localization of the Lesions of Phthisis, London, J. & A. Churchill, Ltd., 1888.

and posterior part of the lower lobe is a spot only second in point of vulnerability to the apex itself."

Of greater significance, however, than cases of secondary involvement of the lower lobe in the course of a progressive lesion of the upper lobe are those cases in which the lesion of the lower lobe represents the initial manifestation of bronchogenous tuberculosis. It is of interest to note that Kidd [13] as early as 1886 emphasized the importance of the apex of the lower lobe as a site of predilection for early tuberculous changes, in contrast to the base of the lung. This author called attention to the fact that while lesions in the latter location are extremely rare, the former region is "very prone to disease and may be attacked before the apex of the upper lobe." More recently the significance of the apex of the lower lobe as a site of early changes has been stressed by Graeff and Kuepferle,[7] Pohl [14] and Assmann.[15] Sweany, Cook and Kegerreis [16] called attention to the situation of early cavities in that area. Other observations on tuberculosis of the lower lobe and basal tuberculosis were contributed by Rosenblatt,[17] Middleton,[18] Dunham and Norton,[19] Colton [20] and Jacob.[21]

This study is based chiefly on the material of the department of tuberculosis of the Metropolitan Hospital over a period of four years. The prime object of investigation were the cases which presented sufficiently definite evidence that the process actually began in the lower lobe. There were thirty-four cases of this group, which will be referred to here as cases of primary lesions of the lower lobe. (The term primary in this connection is not to be confused, of course, with the primary tuberculous infection.) In an appreciable number of additional cases the evidence in favor of the origin of the lesion in the lower lobe was equivocal because of the advanced phase of the disease. There was also a small group of cases showing either very slight apical

13. Kidd, P.: On Basic Tuberculous Phthisis, Lancet **2**:615 and 665, 1886.

14. Pohl, R.: Ueber die Formen der bronchogenen Phthise mit Beginn im Unterlappen, Beitr. z. Klin. d. Tuberk. **69**:229, 1928.

15. Assmann, H.: Frühinfiltrat, Ergebn. d. ges. Tuberk. **1**:115, 1930.

16. Sweany, H.; Cook, C. E., and Kegerreis, R.: A Study of the Position of Primary Cavities in Pulmonary Tuberculosis, Am. Rev. Tuberc. **24**:558 (Nov.) 1931.

17. Rosenblatt, J.: Chronic Pulmonary Tuberculosis Primarily in the Lower Lobe, J. A. M. A. **76**:1647 (June 11) 1921.

18. Middleton, W. S.: Lower Lobe Pulmonary Tuberculosis, Am. Rev. Tuberc. **7**:307 (July) 1923.

19. Dunham, K., and Norton, V. V.: Basal Tuberculosis, J. A. M. A. **89**: 1573 (Nov. 5) 1927.

20. Colton, W. A.: Basal Lesions in Pulmonary Tuberculosis with Report of 7 Cases, U. S. Vet. Bur. M. Bull. **4**:503 (June) 1928.

21. Jacob, M.: Lower Lobe Pulmonary Tuberculosis, M. J. & Rec. **129**:32 (Jan. 2) 1929.

changes of abortive character or nodular productive disseminations of the type seen in the chronic hematogenous forms,[22] which subsequently developed into progressive lesions of the lower lobe. These cases presented thus a transition from the latent and benign type into progressive caseous-cavernous phthisis of the lower lobe. Finally, the mode of secondary involvement of the lower lobe was studied in many cases of lesions of the upper lobe in which the subsequent stages of progression could be observed. It may not be amiss to point out that, owing to the character of the material of our institution in which the advanced forms show a decided predominance, the proportion of cases with early involvement is rather limited. It is probable, therefore, that given a different type of material the number of cases with initial lesions of the lower lobe would be considerably augmented.

INCIDENCE AND CLINICAL FEATURES

In the group of cases with primary involvement of the lower lobe there was found a remarkable predominance of females. In a total of thirty-four cases there were twenty-eight women and only six men. This predominance of the female sex, impressive as it is in itself, becomes particularly striking when the relations to the total number of patients admitted during the same period are considered. Taking as a basis the material from the service of the Metropolitan Hospital, from which the bulk of the instances have been collected and where the incidence could be checked against the total number of patients, the following figures were obtained: Of twenty-seven patients twenty-three were women and only four, men—a ratio of approximately 6:1 in favor of the former. The total number of patients with pulmonary tuberculosis admitted during the same period was 4,494, of whom approximately three-fourths were males and only one-fourth females. According to this calculation, involvement of the lower lobe was observed in the ratio of about eighteen women to one man on the basis of the total material.

A point which deserves attention is the fact that there were four women in this group in whom the pulmonary lesion developed during pregnancy. A further interesting feature is the presence of three cases of silicosis in the small group of six male patients. In these cases the history and findings indicated that the silicosis preceded the tuberculous involvement. Although it cannot be denied that this may be a mere coincidence, considering the very small number of male patients, there is nevertheless a strong possibility that this factor is of some moment. This point, as well as the significance of pregnancy, will be taken up later in the course of the general discussion.

---

22. Reisner, D.: The Relations Between Extrapulmonary and Pulmonary Tuberculosis, Am. Rev. Tuberc. **30**:375 (Oct.) 1934.

It appears, therefore, that the question as to the relative occurrence of tuberculosis of the lower lobe in the sexes is probably of greater significance than that concerning the total incidence. A true index can be arrived at only by a separate consideration of the male and female material. The occurrence of primary involvement of the lower lobe can thus be regarded as extremely rare in men. In women, on the other hand, although these lesions are by no means common, they seem to represent a distinct entity. It may furthermore be of interest that in the cases in which the lower lobe was found to be secondarily involved the discrepancy between men and women, though still present, was much less apparent.

As to the racial distribution, there were twenty-four white patients as against ten Negroes in this group. This relation corresponds closely with the general distribution of the patients in the institution. Thus, in contrast to the findings of Dunham and Norton,[19] no predominance of the colored race could be noted.

The distribution according to age reveals that about two-thirds of the patients of this group were between 17 and 30 years of age; there was only one patient in the fifth decade of life and two in the sixth, the latter being patients with silicosis. The youngest patient was 17, the oldest 59. The average age of 29 years found in this group does not represent any deviation from the age incidence observed in corresponding forms of pulmonary tuberculosis in general. The statements of some authors (Dunham and Norton[19] and Jacob[21]) who expressed the belief that tuberculosis of the lower lobe is peculiar to juveniles, are not borne out by this series of cases.

An analysis as to the duration of the symptoms revealed that the majority of the cases represented early phases of the disease. In more than one half, or eighteen cases, the patients dated their illness back for a period between two to eight weeks; in four cases the symptoms were present for three months, in nine for a period ranging between four and nine months, and in only three cases could the symptoms be traced back over a period of more than nine months.

The mode of onset, although showing no characteristic features which would definitely distinguish it from the types seen in cases with more common locations of the lesion, was noteworthy because of the rather acute griplike or pneumonia-like syndrome presented by a number of patients in the initial phase of the disease. This, however, is not infrequently observed in the early exudative and caseous forms of tuberculosis in general and cannot be regarded as peculiar to any particular location.

The physical signs are pronounced and easily detectable in the patients who show extensive involvement of the lower lobe. In patients with involvement of a relatively small area, especially in those in whom

the lesion is limited to the apex of the lower lobe, the signs may be peculiarly scant or even completely absent and in marked contrast to the roentgen findings. Several authors attempted to explain this discrepancy on the basis that the lesion is centrally located. This, however, is far from correct, as will be shown presently from the roentgen findings. The area which should be examined with particular attention is the interscapular and paravertebral zone, approximately between the fifth and seventh dorsal vertebrae. This location is most likely to yield positive findings in these cases. On the other hand, it is important to point out that certain physical findings obtained in this area are apt to be misleading, and that particular care must be exercised in their evaluation. Because of the vicinity of the vertebral column and of the trachea and large bronchi, alteration of the percussion note and breath sounds is frequently found here in normal subjects.

A further point of interest is a distinct predominance of the right side in lesions of the lower lobe. There were twenty-four patients with lesions on the right side, as against ten in whom the left side was involved. The preference for the right side could be observed to an equal extent in patients with lesions of the upper lobe in whom the lower lobe, especially its apex, became secondarily involved.

ROENTGEN FINDINGS

In analyzing the roentgen findings in tuberculosis of the lower lobe a definite distinction must be made between cases in which there is massive involvement and those in which the lesion is confined to a more or less limited area. In the former the findings are, as a rule, obvious, and the location in the lower lobe can easily be identified as such, while the latter often require painstaking study. Careful fluoroscopic observation, as well as exposures in the oblique and lateral views, are in most instances indispensable for exact determination of the nature and location of the changes.

Of the group of patients presented in this report only a small number showed extensive involvement of the lower lobe. These were patients with more or less acute caseous pneumonic lesions frequently showing rapid progression (fig. 1). Occasionally the lower lobe appears markedly diminished in size. This may occur either in the more chronic cases with cirrhotic contraction or in cases in which the tuberculous process is combined with lobar atelectasis, as is sometimes seen in aspiration following hemoptysis. In such cases the outer margin of the lower lobe can be seen in the sagittal view as a sharp oblique line running from the hilar area outward and downward toward the base. If the lower lobe of the right lung is involved the findings are evident. On the left side the involved lobe may be concealed behind the heart

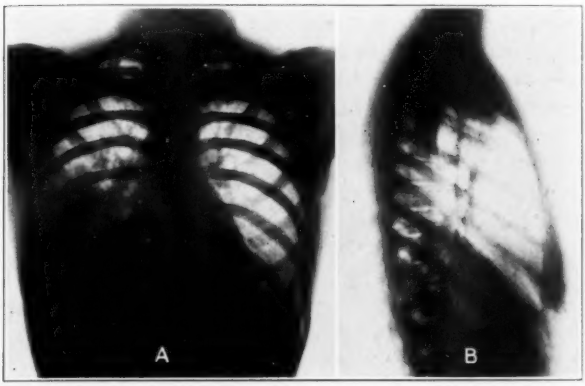

Fig. 1 (female, aged 19).—Roentgenograms showing massive tuberculous pneumonia of the lower lobe of the right lung with probable cavitation at its apex. The lateral view (*B*) demonstrates that the lesion stops abruptly at the interlobar fissure; the heavy density along the margin of the lower lobe is due in part to the superimposed cardiac shadow.

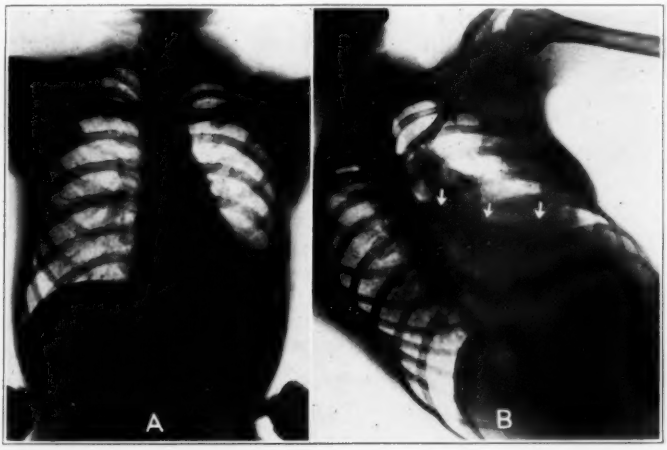

Fig. 2 (female, aged 17).—Roentgenograms showing infiltration of the lower lobe of the left lung, with probable atelectasis following hemoptysis. The postero-anterior view (*A*) shows only indefinite clouding at the base; note the retraction of the mediastinum and heart to the left. The roentgenogram taken with the patient leaning over to the left and in a slightly oblique position (*B*) shows the contracted lower lobe of the left lung as a sharply defined triangular basal shadow with a translucent area in the subapical portion indicating a cavity. These findings were subsequently confirmed after pneumothorax had been established.

shadow, and additional positions have to be employed in order to demonstrate the lesion (fig. 2). Such findings resemble the triangular basal or retrocardiac shadows occasionally observed in chronic nontuberculous basal lesions.

The predominant majority of patients, however, present involvement of a limited area of the lower lobe, almost invariably of its apical or subapical portion. In practically all the patients of this group there were found cavitations of appreciable size at the time of the first examination; only a very few could be seen in the precavernous stage. This is of considerable interest in view of the brief duration of the symptoms in most cases and indicates that lesions in this location have a decided tendency toward early ulceration and cavity formation. The so-called benign exudative forms which frequently show a great deal of absorption could not be observed in this location.

Changes situated in the apical portion of the lower lobe as a rule appear close to or directly over the area of the root in the roentgenogram taken in the sagittal direction, thus frequently giving the impression of a lesion extending from the hilus. However, further views in other planes reveal that this is merely due to overlapping of densities not related to each other. In the lateral position the infiltration or cavitation is usually seen near the dorsal wall of the chest, not far from the pleural surface projecting over the vertebral column, which indicates that the actual location is in the paravertebral posteromedial zone. Lesions situated at some distance from the apex appear to be farther lateral from the area of the root. In the majority of cases the lesion appears in the sixth or seventh posterior interspace as projected on the wall of the chest. This corresponds with the interscapular area previously mentioned as the most important point where physical signs should be looked for. On the right side the location is frequently somewhat lower than on the left, this evidently being due to the fact that the lower lobe of the right lung is, as a rule, smaller than that of the left. A further important finding is the sharp demarcation of the superior margin of the lower lobe, which can frequently be demonstrated in the oblique or lateral view. This is the case when the process reaches the lobar margin and the adjacent portion of the interlobar pleura (figs. 3 and 4).

The cavities often present the appearance of the thin-walled elastic variety seen in early lesions, or they are surrounded by a zone of exudative infiltration. Because of the apparent proximity to the root their identification is not infrequently difficult. The markings radiating from the hilus and the fact that the boundaries of the annular shadow are partly concealed behind the structures of the root may often be confusing in attempting their exact identification. On the left side the

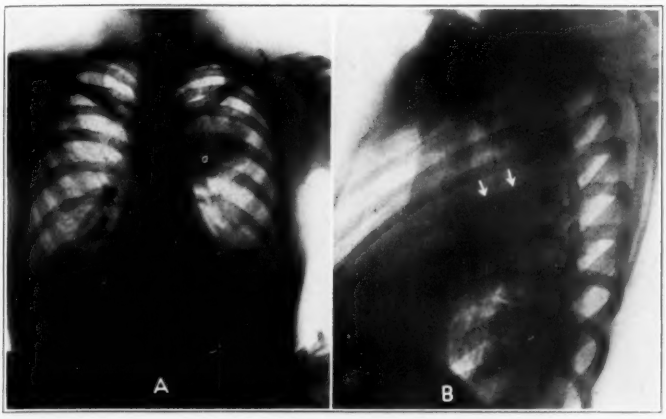

Fig. 3 (female, aged 20, pregnant).—Roentgenograms showing exudative infiltration at the apex of the lower lobe of the left lung. The postero-anterior view (*A*) shows the density apparently extending from the hilus. The postero-oblique projection (*B*) demonstrates the location in the apex of the lower lobe, with a sharp demarcation of the lobar margin.

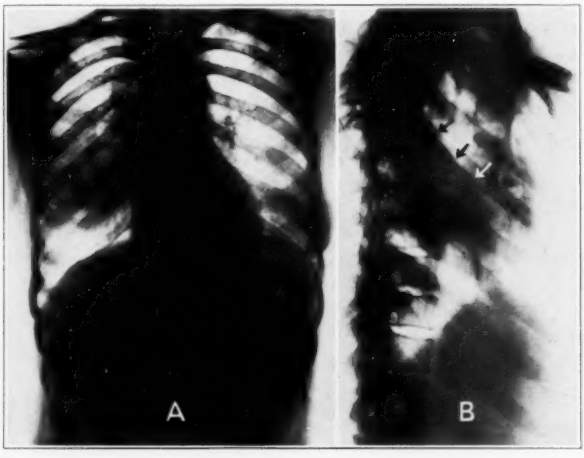

Fig. 4 (female, aged 31).—Roentgenograms showing a large area of pneumonic infiltration in the midfield of the right lung. The postero-anterior view (*A*) shows the density apparently connected with the area of the root and the cavity projecting into the sixth posterior interspace. The lateral view (*B*) demonstrates the lesion in the superior portion of the lower lobe, with a sharp demarcation of its margin and the cavity over the sixth dorsal vertebra. There is a deformity of the upper part of the dorsal spine due to old tuberculous caries.

cavity may easily be concealed behind the shadow of the heart. Fluoroscopic studies and additional views, as has already been mentioned, frequently prove of great value (figs. 5, 6 and 7). The demonstration of a fluid level is extremely helpful in these cases. It is of interest that retention of fluid was far more frequently observed in cavities of the lower lobe than in those of the upper lobe. The collection of fluid may be large, and the cavity may thus resemble a nontuberculous abscess

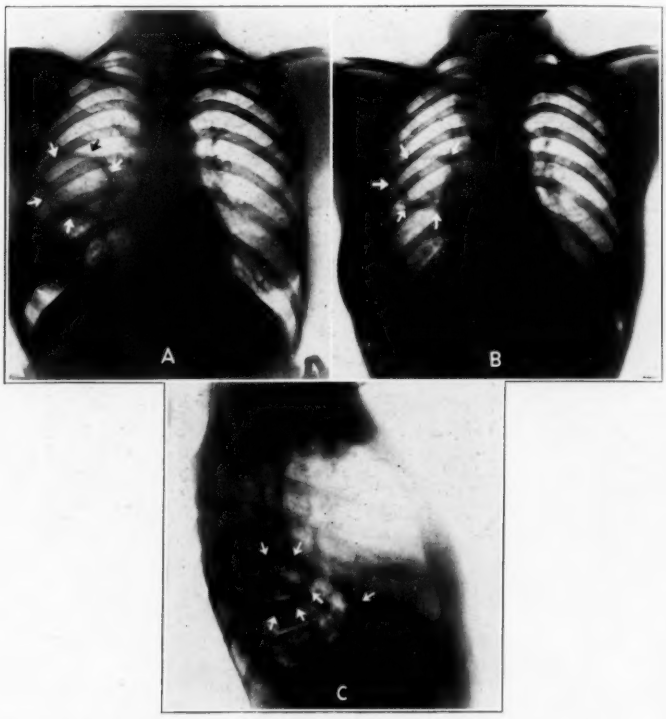

Fig. 5 (female, aged 26).—The postero-anterior view (*A*) shows a large cavity in the midfield of the right lung close to the hilus, with focal infiltration down to the base. The antero-posterior exposure (*B*) demonstrates the cavity more clearly defined and smaller, indicating its posterior location. The lateral view (*C*) shows the cavity close to the posterior wall of the chest, over the spinal column, located in the apex of the lower lobe; there is infiltration along the lobar margin down to the diaphragm.

(fig. 8). The reason for this is evidently the fact that the anatomic position of the bronchi renders conditions of drainage less favorable in this location than in cavities situated in the upper lobe.

Cavities located in the apex of the lower lobe are remarkable for the large size which they seem to attain within a comparatively short period. In this connection it may be of interest to cite an observation of Aschoff,[23] who found that the reinfection foci situated in more caudate portions of the lung are, as a rule, larger than those located nearer the summit. This was also observed by Assmann [15] in roentgenologic studies of early infiltrations. It should not be overlooked, of course, that the routine roentgenogram taken in the dorsoventral position is bound to exaggerate the size to a certain extent because of the location of the apex of the lower lobe close to the posterior wall of the chest. In cavities projecting near the root on the right side their relation to the interlobar fissure between the upper and middle lobes should be noted. If the horizontal fissure line is seen extending across the annular shadow

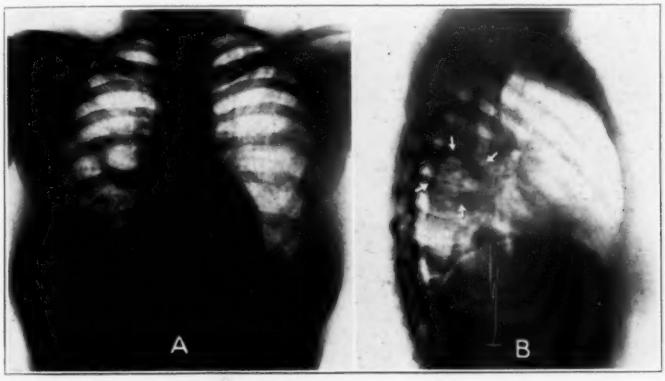

Fig. 6 (female, aged 26).—The postero-anterior view (*A*) shows a cavity on the right side directly over the hilus and focal infiltration through the lower half of the right lung and in the midfield of the left lung. Note the crossing of the cavity by the line of the interlobar fissure. The lateral view (*B*) demonstrates the cavity posteriorly over the spinal column, the location corresponding with the apex of lower lobe. There is a small collection of air posteriorly and above the diaphragm, due to initial pneumothorax.

this is practically a conclusive sign that the cavity is situated posteriorly within the apex of the lower lobe (fig. 6).

That the apex and subapical area of the lower lobe represent a distinct site of predilection for tuberculous involvement is also demonstrated in patients with more or less acute and massive lesions of the lower lobe in whom the earliest as well as the largest cavitations are, as a rule, found at or near the apex. In such cases the cavity may

23. Aschoff, L.: Ueber den phthisischen Reinfekt der Lungen, Klin. Wchnschr. **8**:1 (Jan. 1) 1929.

extend directly from the apex of the lower lobe into the adjoining area of the upper lobe. The preference for the apical region holds true to an equal extent for secondary changes of the lower lobe which occur in the course of a progressive lesion of the upper lobe.

In the group of cases of primary tuberculosis of the lower lobe there were only a few instances in which the lesion remained limited

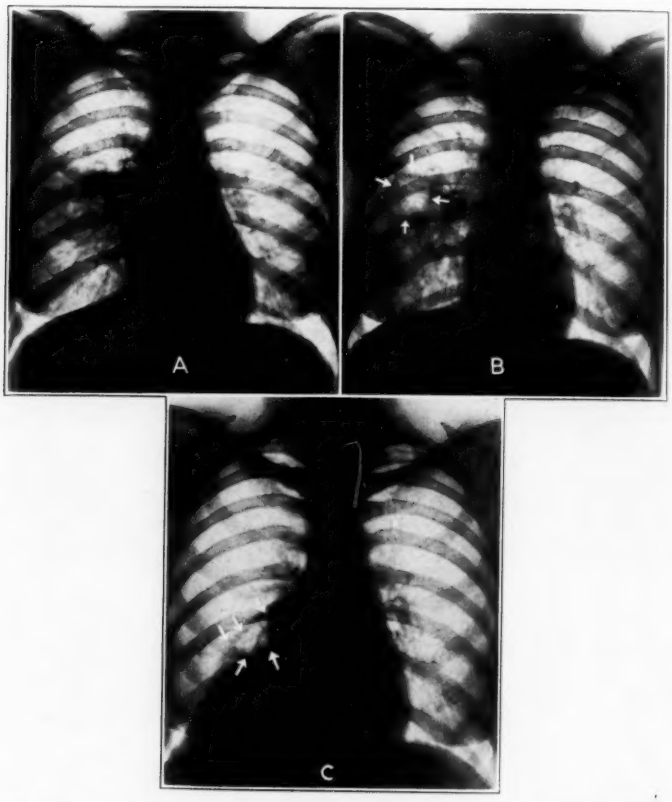

Fig. 7 (female, aged 19).—*A* shows exudative infiltration in the midfield of the right lung, apparently extending from the hilus. Three months later (*B*) there was a distinct cavity, with focal spread to the base. After pneumothorax had been instituted (*C*) there was selective collapse of the lower lobe; the cavity is distinctly seen at its apex.

to the originally involved area for any length of time. In most cases there occurred a bronchogenous spread into other portions of the lung A fairly characteristic and frequently encountered mode of spread is a

more or less diffuse distribution of foci of the acinous or sublobular type through the remaining area of the lower lobe, often extending down to the extreme base (figs. 5 and 6). This represents a spread by aspiration through the bronchial ramifications of the lower lobe. Other common sites of secondary involvement are the peripheral portions of the upper lobes in the vicinity of the lobar margins, more often from the right to the left side than vice versa. Secondary involvement of the apex of the upper lobe is also not infrequently observed.

It is very probable that the unfavorable conditions of drainage of the apical branches of the bronchus of the lower lobe and the resulting stagnation of infectious material in the cavities play a rôle in promoting spread by aspiration. In cases with a bronchogenous spread in the

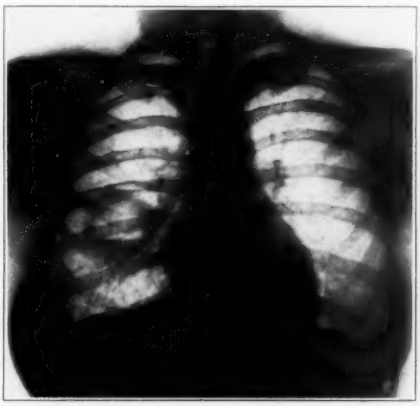

Fig. 8 (female, aged 26).—Roentgenogram showing an early tuberculous cavity in the midfield of the right lung close to the area of the root, with a collection of fluid resembling a nontuberculous abscess; there were no other pulmonary findings. Note the crossing of the cavity by the interlobar fissure, as in figure 6. Further study revealed that the cavity was located in the apex of the lower lobe.

cranial direction from the cavity the cough may be an important factor, a point particularly stressed by Tendeloo.[8] It is evident that lesions of the lower lobe in the advanced stages with extensive progression may present an appearance which is hardly characteristic. In the absence of a preceding follow-up series a spread from above downward is easily assumed in such instances (fig. 9).

Occasionally tuberculous infiltration involving other pulmonary areas than the cranial portion of the lower lobe may also give rise to the roentgen appearance which resembles a hilus lesion. This is the case if the changes are situated in the medial portions of the upper lobes

and near their margins, in the middle lobe of the right lung or in the lingula of the upper lobe of the left lung. These locations, however, represent, as a rule, secondary manifestations of progressive bronchogenous tuberculosis. The possibility of localized interlobar or paramediastinal pleurisy may also have to be considered. In such instances further study in various positions demonstrates the respective lobar relations of the lesion in question.

In the vast majority of cases a thorough roentgen examination will reveal the nature of the changes giving the appearance of the so-called hilus lesions. It will demonstrate that such findings in reality represent merely parenchymal changes which happen to be situated in certain regions of the lung, but are otherwise not characteristic or essentially different from corresponding forms of tuberculous changes elsewhere

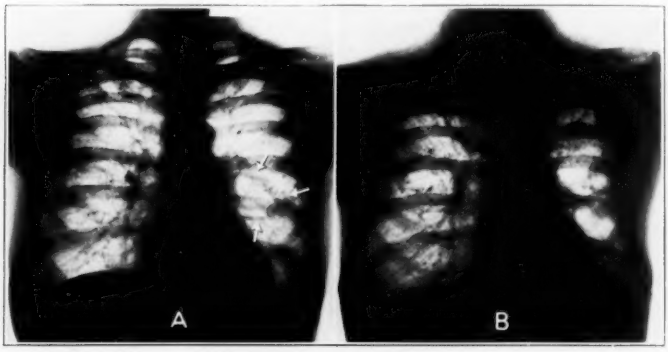

Fig. 9 (female, aged 32).—*A* shows a large cavity in the region of the left hilus (arrows), located in the superior portion of lower lobe, and a smaller cavity farther down and lateral. There were a few soft foci in the upper lobe of the right lung and scattered old calcified nodules in both lungs. Three years later (*B*) there were extensive infiltration and cavitation of the upper lobe of both lungs; the lower lobe of the left lung appeared contracted, and the cavity was surrounded by a dense wall.

in the lung. Of course, the possibility of enlarged tracheobronchial lymph nodes as the basis for the roentgen findings will have to be excluded. It seems fair to state, therefore, that, so far as adult tuberculosis is concerned, there are very few instances in which the findings obtained after an exhaustive roentgen analysis still justify the assumption of some anatomic or pathogenetic relationship with the hilar structures. This is entirely in agreement with the opinion expressed by Fleischner [10] and substantiated by postmortem observations, as was mentioned at the outset of this paper.

PROGNOSIS AND THERAPY

In answering the question whether or not there are any distinct differences with respect to the prognosis between tuberculosis of the lower lobe and the more common lesions of the upper lobe, certain limitations must not be lost sight of. In the first place, because of the comparatively small number of cases of primary involvement of the lower lobe the value of data gathered by a single observer is necessarily limited. Secondly, the measures of collapse therapy which most of the patients undergo are naturally bound to alter the spontaneous course of the disease. There are, nevertheless, several points which should be stressed here. The prognosis in pulmonary tuberculosis depends largely on the anatomic character of the lesion and the extent of the involvement. It is therefore important to recall, as has already been stated, that practically all the patients, of this group exhibited changes of the caseous-cavernous form, and that the cavitations seem to develop in the early phase of the disease and attain a rather large size. Furthermore, there is a distinct tendency toward further spread, with frequent involvement of the contralateral lung. In general, however, the course and ultimate fate in cases of lesions of the lower lobe are probably not different from those in cases in which the lesion originates in the upper lobe, provided that the nature and extent of the involvement are of a corresponding type, a point also noted by Pohl.[14] True, in several cases of this series there could be observed massive caseous pneumonic lesions of the lower lobe, with rapid progression and a fatal event after a comparatively brief period of illness. The identical course, however, may take place if a lesion of a similar type involves the upper lobe.

Considering thus the character of the lesion, it is evident that early application of measures to bring about a collapse of the diseased portion of the lung is most essential. As to the procedure to be adopted, artificial pneumothorax seems to offer the best results. Because of the location in the lower lobe, phrenic neurectomy was employed as the initial measure in eight cases of this group; a satisfactory result with closure of the cavity was obtained in one instance only. Pneumothorax was instituted in nineteen of thirty-four cases of primary lesions of the lower lobe. In eleven cases a satisfactory result was obtained. In one case the result was doubtful, and in one case pneumothorax had to be discontinued because of circulatory embarrassment. In six cases the result was considered unsatisfactory because of failure to obtain closure of the cavities. It is interesting to note that in several instances in the group of failures, although no demonstrable adhesions were present, the cavities could not be collapsed. This behavior may have some connection with the location of the lesion, although no adequate explanation can be offered as yet.

It appears, therefore, that, with the possible exception of actual basal locations, artificial pneumothorax is the procedure of choice in lesions of the lower lobe as well as in those of the upper lobe. If pneumothorax is not feasible or if the results are unsatisfactory more radical measures of surgical collapse should be employed.

COMMENT

In discussing the problem of tuberculosis of the lower lobe the question arises whether such locations represent nothing further than occasional atypical occurrences which are merely exceptions to the general rule. That this is evidently not the case is indicated by the almost invariable location of the early changes in a distinct portion of the lower lobe, that is, in its apical or subapical area, and furthermore by the curious predominance of these lesions in women. These facts are so striking that they call for an explanation.

It is an indisputable fact as well as a matter of common knowledge that there are certain regions of the lung which are more prone to tuberculous involvement than others. It is likewise well established that the primary focus in childhood shows a decidedly different location in the lung than the early manifestations due to reinfection or superinfection in adult life. To be sure, the question as to what constitutes these differences in susceptibility has not been answered to complete satisfaction as yet. It lies beyond the scope of this paper to enter into a full discussion of the theories which have been advanced on this subject. It is probable, however, that the responsible factors are intimately related to the anatomic configuration of the adult thorax, as contrasted with the type seen in children; furthermore, that the physiologic mechanism of respiration is of considerable influence. It seems most plausible that the restricted ventilation and consequent impairment of the circulation of the blood and lymph in certain parts of the lung create particularly vulnerable areas.

Of more immediate concern, however, in connection with the subject of this paper is the question of the topographic definition of the predisposed region of the lung. To begin with, it is important to point out that the significance attached to the apex as a site of initial manifestations of progressive forms of the adult type of tuberculosis has unquestionably been overemphasized in the past. In view of the present knowledge, it would seem far more correct to use the broader term cranial zone instead. What are the anatomic boundaries of this zone? According to Tendeloo,[8] the area of predisposition comprises the cranial fourth of the lung. This author states that there is a minimum of variation in respiratory volume in this region, especially in the posterior

and paravertebral zone. Macklin [24] also called particular attention to the marked limitation of expansile movements in the posterior paravertebral region which lies above and behind the hilus almost completely surrounded by the rigid structures of the thorax. The area designated by Macklin as the superoretroradicular region coincides closely with that defined by Tendeloo. It is thus evident that the area in question includes a considerably larger portion than the apex of the upper lobe. Tendeloo regarded the fifth rib as its inferior boundary, which makes it practically identical with Macklin's superoretroradicular region. It is of particular significance to point out here that both these authors stressed the fact that the apex of the lower lobe forms a part of this zone.

It appears, therefore, that the region particularly prone to tuberculous involvement includes the posterior aspect of the upper lobe and the apex of the lower lobe. That the dorsal portion of the upper lobe represents the most common location of the initial changes is borne out by roentgenologic studies of early cases, as well as by observations at necropsy. This was long ago clearly demonstrated by Birch-Hirschfeld [25] and more recently again emphasized by Loeschcke.[26] Assmann [15] pointed out that the location of the infraclavicular infiltrates corresponds with the dorsal subapical region of the upper lobe, and Sweany, Cook and Kegerreis [16] recently called attention to the posterior location of nearly all early cavities. The apex of the lower lobe, however, represents a comparatively infrequent location of early lesions, if taken by and large in relation with the frequency of involvement of the upper lobe. It seems, therefore, that, generally speaking, there is a better chance for the apex of the lower lobe to escape involvement, and that the operation of certain additional factors may be necessary in order to bring about the development of a lesion in that location.

What are the conditions that may enhance the susceptibility of this region of the lung? It is important to recall here that the lower lobe and the dorsal portion of the upper lobe are expanded mainly by the diaphragmatic movements, in contrast to the greater portion of the upper lobe (on the right side also the middle lobe), which is acted on by the costal mechanism (Keith [27]). The action of the diaphragm, however, is exerted chiefly on the caudal and lateral portions of the lung and decreases progressively in the direction from the base toward

24. Macklin, C. C.: The Dynamic Bronchial Tree, Am. Rev. Tuberc. **25**:393 (March) 1932; Bronchial Length Changes and Other Movements, Tubercle **14**: 16 and 69, 1933.

25. Birch-Hirschfeld, F. V.: Ueber den Sitz und die Entwicklung der primären Lungentuberkulose, Deutsches Arch. f. klin. Med. **64**:58, 1899.

26. Loeschcke, H.: Ueber das Wesen der Lungenspitzendisposition zur Tuberkulose-Erkrankung, Beitr. z. Klin. d. Tuberk. **64**:344, 1926.

27. Keith, A.: The Mechanism of Respiration in Man, in Hill, Leonard: Further Advances in Physiology, New York, Longmans, Green & Co., 1909.

the summit. The degree of diaphragmatic respiration is thus in an inverse ratio to the distance from the base. This may have a bearing on the fact that the location of early lesions diminishes in frequency from above downward.

The location of the upper limit of the area expanded by the diaphragm depends probably to a great extent on individual variations. Tendeloo [8] placed this limit at the level of the fifth rib, which is evidently intended to indicate an average. There is no doubt, however, that there are variations in the upward or downward direction according to the extent of diaphragmatic movements. The apex of the lower lobe represents thus a borderline zone, and it depends largely on the effectiveness of the diaphragmatic function whether or not this region is included within the range of the area of lessened resistance.

It seems probable that this mechanism has an important bearing on the question of involvement of the lower lobe in tuberculosis and, more specifically, on the striking finding that this occurs predominantly in females. The difference in the type of respiration in men and women seems to offer a plausible explanation. It is a matter of common knowledge that in men the lung is expanded chiefly by the diaphragmatic movements, whereas in women the costal type of breathing is the predominant factor. A lucid description of these respiratory types was given by Hutchinson [28] as early as 1846 and more recently by other writers, especially de la Camp [29] and Keith.[27] The variations in the behavior of the diaphragm are most convincingly demonstrated on fluoroscopic observation.

In view of the more limited diaphragmatic excursions in women, it is only logical to assume that the superior boundary of the pulmonary area ventilated by the diaphragm is, on an average, at a lower level in women than in men. It is, therefore, reasonable to expect that the zone of predisposition comprises a larger area in the former and that it extends farther down, including a portion of the lower lobe, chiefly its apical region.

Thus, with all other factors remaining equal (as an equal infective dose and an equal state of immunity), there seems to be a considerably greater chance for involvement of the lower lobe in women than in men. It goes without saying, of course, that in the vast majority of cases the early changes are found in the upper lobe in women as well. However, while in men the lower lobe is, as a rule, better equipped to withstand the injurious effect, in women its superior portion seems to

28. Hutchinson, J.: On the Capacity of the Lungs and on the Respiratory Function, Med.-Chir. Tr., London **29**:137, 1846.

29. de la Camp: Beiträge zur Physiologie und Pathologie der Zwerchfellathmung, einschliesslich der zugehörigen Herzbewegungen, Ztschr. f. klin. Med. **49**: 411, 1903.

represent a distinct part of the vulnerable zone, though to a lesser degree than the upper lobe. It is thus perhaps merely a matter of accident if this portion becomes involved in preference to more common locations. It cannot be denied, however, that additional factors, such as an increase of the infective dose beyond a certain threshold or a diminished state of resistance, may be necessary in order to produce changes in this ordinarily less susceptible region of the lung.

A further point which supports the conception just outlined is the fact that in some cases of this group the lesion developed during the course of pregnancy. Although this combination was present in only a few instances, it nevertheless deserves attention, considering the rather infrequent occurrence of lesions of the lower lobe in general. It is also of interest to note that among the very few cases of initial involvement of the lower lobe recorded from postmortem observations there were two instances which concerned pregnant women (Birch-Hirschfeld [25] and Beitzke [30]). The elevation of the diaphragm and its restricted movements on quiet breathing which take place in pregnancy cause impaired ventilation of the lower lobe, which is especially pronounced in its apical area, thus accentuating the already preexisting unfavorable conditions in women. An additional factor which may also have some effect is a relaxation of the tension exerted by the diaphragm on the summit of the lung (Orsós [31]) as a result of increased intra-abdominal pressure. The combination of these factors is apt to favor a downward shift of the predisposed zone.

Another significant finding which seems to point in the same direction is the predominance of lesions of the lower lobe on the right side. This is striking in view of the fact that there is no definite preference for the right side in the reinfection forms of pulmonary tuberculosis as a whole. It is possible that the higher position and more limited excursions of the right side of the diaphragm may operate as contributing factors. There is also a possibility that the anatomic course of the right main bronchus, which runs in a more straight line in relation to the trachea, may to a certain extent favor an aerogenous infection of the right lung. In this respect the lesions of the lower lobe show a certain parallel with the primary infection, which also seems to have a preference for the right lung (Pagel and Henke [32] and Stoloff [33]).

30. Beitzke, H.: Pathologische Anatomie der Lungentuberkulose im Pubertätsalter, Ergebn. d. ges. Tuberk. **3**:1, 1931.

31. Orsós, F.: Die generelle mechanische Disposition der Lungenkuppen zur Tuberkulose, Beitr. z. Klin. d. Tuberk. **70**:504, 1928.

32. Pagel, W., and Henke, F.: Lungentuberkulose, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 3, pt. 2.

33. Stoloff, E. G.: Primary Infection in Tuberculosis, Am. J. Dis. Child. **33**: 363 (March) 1927.

There are undoubtedly other factors than those directly related to the respiratory mechanism that may promote the development of a tuberculous lesion in unusual locations. The possibility that such factors may be present should be especially considered when these lesions are found in male patients. The cases of silicosis observed in this series offer an interesting example in this connection. It seems likely that the block of lymph vessels and the impairment of lymphatic drainage which take place in this condition affect the defense mechanism of the lung and cause a complete alteration in the range of susceptibility of its various regions. Subsequent tuberculous infection may thus lead to atypically located lesions in such cases. Gardner [34] recently called attention to the fact that tuberculous changes complicating silicosis frequently occur in atypical areas, especially in the middle or lower pulmonary field. The occurrence of atypical forms and locations of pulmonary tuberculosis in diabetes is an example of a different nature. It is possible that a change in tissue reactivity resulting from the metabolic disorder may be of significance in furthering such developments. Tuberculous lesions in uncommon locations are also not infrequently met with in persons of advanced age and in patients with kyphosis or kyphoscoliosis (von Hansemann,[35] Ranke,[36] Loeschcke [26]). In these conditions, however, the responsible factors are probably related to the altered configuration of the thorax and its effect on the respiratory mechanism, as was particularly emphasized by Loeschcke.

Finally, it must be mentioned that there occur various transitional respiratory types in both sexes, depending on the general constitutional habitus, such as a predominantly diaphragmatic type of breathing in women or a chiefly costal type in men. The latter fact may be of some consequence with respect to the sporadic occurrence of lesions of the lower lobe in males. However, it seems reasonable that the chances for development of tuberculosis of the lower lobe are far greater in women, as they are under a distinct potential disadvantage which is evidently determined by physiologic limitations.

In conclusion, a few remarks should be made regarding the clinical differential diagnosis of tuberculosis of the lower lobe. It has been variously stated that lesions of the lower lobe must be considered nontuberculous unless proved otherwise. This is probably true, so far as strictly basal locations are concerned. In such cases definite clinical or roentgenographic features indicative of tuberculosis may be absent,

34. Gardner, L. U.: Inhaled Silica and Its Effect on Normal and Tuberculous Lungs, J. A. M. A. **103**:743 (Sept. 8) 1934.

35. von Hansemann, D.: Ueber typische und atypische Lungenphthise, Berl. klin. Wchnschr. **48**:1 (Jan. 2) 1911.

36. Ranke, K. E.: Die Tuberkulose der verschiedenen Lebensalter, München. med. Wchnschr. **60**:2153 (Sept. 30) 1913.

rendering differentiation from other chronic pulmonary lesions at times difficult. However, purely basal locations without involvement of other portions of the lung are extremely rare. On the other hand, a tuberculous lesion involving the apex of the lower lobe or a massive process of the lower lobe seldom offers serious differential diagnostic difficulties, as these conditions almost invariably present features of the progressive and caseous-cavernous forms with tubercle bacilli in the sputum.

Occasionally, if the patient is seen in the early phase of the disease before any breaking down has taken place, the possibility of nontuberculous bronchopneumonia, as it occurs in grip, may have to be entertained for a while, especially since the onset may be similar in both conditions. More from the roentgenologic than from the clinical standpoint the possibility of neoplasm or abscess may also have to be considered, the former because of the apparent proximity of tuberculosis of the lower lobe to the area of the root, the latter in cases in which there is a solitary cavity with collection of fluid and no other changes in the vicinity. However, only exceptionally will real difficulties arise if all the available clinical and roentgenologic data have been properly evaluated. Of paramount importance is, of course, a careful search of the sputum for tubercle bacilli, no matter how unusual or atypical the location of the process may seem.[37]

SUMMARY AND CONCLUSIONS

The subject of pulmonary tuberculosis of the lower lobe in adults is presented with particular attention to the early reinfection changes occurring in that location.

Strictly basal tuberculosis must be differentiated from lesions involving the superior portion of the lower lobe. Early changes limited to the base of the lung are extremely rare, whereas the apical and subapical regions of the lower lobe represent a typical site of predilection for initial manifestations in the adult form of phthisis. This area is also a fairly frequent location of early bronchogenous metastases in progressive tuberculosis of the upper lobe.

The tuberculous changes occurring in the apex of the lower lobe are almost invariably of the exudative and caseous type, with early cavity formation. Collapse therapy is the only effective treatment, and

37. Since this paper was submitted for publication, twenty-two additional cases of tuberculosis of the lower lobe could be observed. This brings up the total number of patients of this series to fifty-six. Of these, forty-five were females and eleven were males. Among the additional five male patients, two had diabetes and in one patient there was a combination with silicosis. In the additional group of seventeen female patients, there were two instances of diabetes. The ratio between males and females based on the total series shows no material change, as compared with the results originally obtained.

artificial pneumothorax is the procedure of choice, despite the location in the lower lobe.

The roentgen findings in tuberculosis of the lower lobe are discussed, and it is emphasized that changes in its apical region frequently present the misleading appearance of so-called hilus lesions. It is also stressed that in general there is no adequate foundation for the conception of a hilar form of pulmonary tuberculosis as a pathogenic entity.

Tuberculosis of the lower lobe occurs principally in women and is very uncommon in men. An explanation of this difference in the behavior of the sexes has been attempted on the basis of existing physiologic variations in the respiratory mechanism.

2 East Eighty-Fifth Street.

STAB WOUNDS OF THE HEART

A STUDY OF ELECTROCARDIOGRAPHIC CHANGES, POLYSEROSITIS (PICK'S SYNDROME) AND PERICARDITIS

JOHN D. KOUCKY, M.D.
AND
GEORGE MILLES, M.D.
CHICAGO

Since the report of the first case by Cappelen in 1895 and that of the first case with recovery by Rehn in 1896,[1] innumerable instances of surgical repair of wounds of the heart have been recorded. Indeed, this life-saving procedure has become so commonplace that reports of cases limited to the surgical aspects add little to the literature on the subject which Lockwood [2] reviewed exhaustively. This case is reported because it presents certain features which are worthy of study. In the first place, a series of electrocardiograms was obtained, and as relatively few electrocardiographic studies have been made in cases of wounds of the heart, a summary and comparison of all such reports appear to be of value. Second, the case is of interest in that it serves to substantiate and elucidate further the findings of Beck [3] and his co-workers in experimental studies of Pick's syndrome in dogs. Finally, it is a case in which life was so close to being extinct that the entire surgical procedure, including the subsequent cutting down on the veins for the injection of saline solution and for transfusion, was performed without either local or general anesthesia.

REPORT OF A CASE

E. G., a 16 year old white boy, was carried into the Lutheran Deaconess Hospital at 10:50 p. m. with a history of having been stabbed with a pocket-knife about ten minutes previously, after which injury he ran about 75 yards and collapsed.

He was in a comatose condition; his lips were faintly cyanotic; his skin was pale, cold and clammy; he was gasping, and his clothes were soaked with blood.

From the Departments of Surgery and Pathology of the University of Illinois College of Medicine, and the Lutheran Deaconess Hospital.

1. Schmidt-Weyland [12] reported his observations in 1931 in a case of surgical repair of a gunshot wound self-inflicted in 1895.

2. Lockwood, A. L.: Surgery of the Pericardium and Heart, Arch. Surg. **18**:417 (Jan., pt. 1) 1929.

3. (*a*) Beck, C. S.: The Effect of Surgical Solution of Chlorinated Soda (Dakin's Solution) in the Pericardial Cavity, Arch. Surg. **18**:1659 (April, pt. 2) 1929. (*b*) Beck, C. D., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome, ibid. **21**:1064 (Dec.) 1930.

The pulse was thready and at times imperceptible, its rate being about 40. A cursory examination revealed an incised wound about 4 cm. to the left of the midsternal line at the level of the sixth rib. The symptoms of obstruction to the venous inflow of the heart, probably the result of rapidly developing hemopericardium, led to a diagnosis of cardiac tamponade, and the patient was hurried to the operating room. On his arrival there, about five minutes after admission, the radial pulse and heart sounds were imperceptible; respiratory movements were absent, and the pupils were dilated and fixed. Indeed, the only signs of life were questionable quivers of the lower lid and of the upper abdominal muscles. It was decided that any delay in treatment, no matter how short, would make death certain. Operation was therefore begun without undressing or moving the patient from the cart, without attempting sterilization of the skin or hands of the operators and with a limited number of instruments. During the course of the operation sterile instruments and dressings were obtained.

The pericardial sac was exposed by a curved incision to the left of the sternum through three costal cartilages with removal of a segment of the sixth costal cartilage. The pericardial sac was markedly distended, and an incised wound was noted on its anterior surface. The wound was enlarged, and about 250 cc. of clotted and liquid blood was evacuated. The absence of bleeding, anesthesia, respiratory movements and sterile surroundings up to this point were more suggestive of an autopsy than an operation. When exposed the heart was observed to be in a state of standstill or prolonged diastole. After it was grasped, a few beats occurred at intervals of two or three seconds. The rate quickly increased to about 120 with a regular rhythm and remained unchanged during the remainder of the operation. Respirations were resumed immediately on evacuation of the pericardial sac. An incised wound about 3 cm. long was observed in the middle third of the anterior wall of the right ventricle 1.5 cm. to the right of, and parallel to, the descending branch of the left coronary artery. In an attempt to control the bleeding from this wound two fingers were inadvertently pushed into the chamber of the right ventricle. The wound was closed with four interrupted catgut stitches, the adjacent coronary artery being avoided. The pericardium was closed tight. The wall of the chest was sutured, and a Penrose drain was inserted to, but not into, the pericardium. At no stage was anesthesia necessary. During the latter part of the operation 500 cc. of physiologic solution of sodium chloride and a solution of 10 per cent dextrose, followed by 500 cc. of citrated blood, were given intravenously. Semiconsciousness returned during the transfusion. The blood pressure, now obtainable for the first time, was 78 systolic and 48 diastolic. The patient was undressed and put to bed. The respiratory rate was 48; the pulse rate, 92, and the axillary temperature, 99 F. One hour later the blood pressure was 100 systolic and 64 diastolic. During the night the patient recovered consciousness and became so restless that morphine had to be administered.

During the next two days his general condition remained only fair, and he was delirious most of the time. Roentgen examination revealed moderate enlargement of the cardiac shadow and a small amount of air in the upper part of the left pleural space. Transfusion of 300 cc. of citrated blood was followed by a moderately severe reaction. About sixty-eight hours after operation the patient's condition suddenly became much worse. The pulse was barely perceptible; the skin became cold and clammy, and nausea and vomiting were severe. Aspiration of 175 cc. of bloody fluid from the pericardial sac resulted in rapid relief from the symptoms of cardiac tamponade. Twelve hours later the syndrome recurred, and aspiration was again required. The fluid now obtained was turbid and contained numerous staphylococci; so the pericardial sac was widely opened. Within twenty-

four hours the exudate from the pericardial sac had become frankly purulent. During this period pulsus paradoxus and at times pulsus alternans were noted.

During the next six days the temperature fluctuated between 98 and 103 F., and the pulse rate, between 88 and 110. The patient was delirious at times and urinated involuntarily. The discharge from the pericardium became thick and purulent. The contractions of the heart churned the fibrinous exudate in the pericardial sac into masses as large as 2 cm. in diameter, which interfered with free drainage from the sac. For this reason irrigations of the pericardial sac with surgical solution of chlorinated soda every two hours while the patient was awake were begun on the tenth postoperative day and were continued with diminishing frequency for eighteen days. These irrigations often produced abdominal and pre-

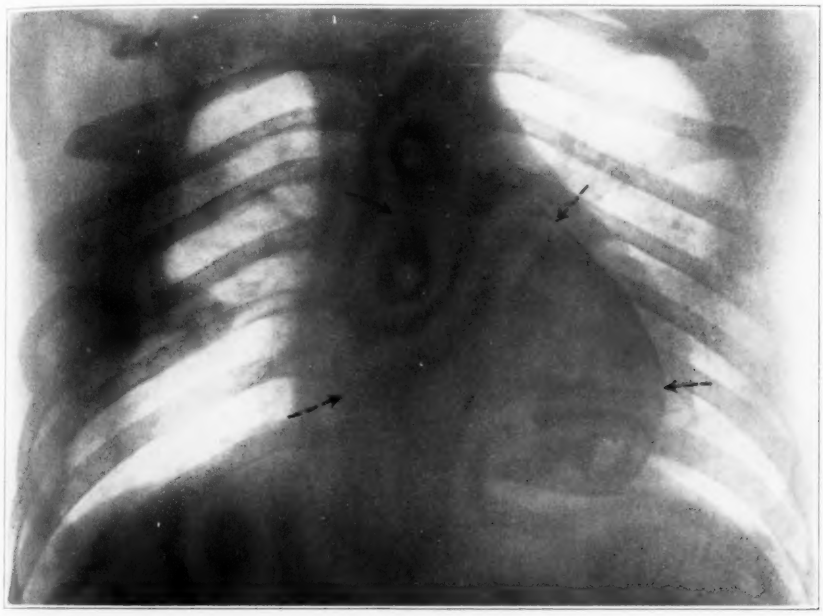

Fig. 1.—Anteroposterior roentgenogram of the chest taken after injection of an iodized and chlorinated peanut oil into the pericardial sac.

cordial pain and distress and were followed within an hour by nausea and occasionally by vomiting.

By the twenty-eighth postoperative day the discharge from the pericardial sac had diminished in amount, and physiologic solution of sodium chloride was substituted for the surgical solution of chlorinated soda in irrigating the sac. At this time curiosity as to the degree of obliteration of the sac prompted us to investigate the matter by injecting an iodized and chlorinated peanut oil into the sac and examining the chest roentgenologically (figs. 1 and 2). The oil was found collected in small pools and distributed unevenly in the sac. None could be seen on the posterior or left wall; it appeared to be confined to an oval area about 7 by 10 cm. at the side of the anterior or right wall of the pericardial sac, and some was collected in the pool at the base of the heart.

On the thirtieth postoperative day, just two days after discontinuation of the irrigations with surgical solution of chlorinated soda, ascites was noted, and the liver was found to be enlarged and tender. An encapsulated hydrothorax appeared at this time, first on the right side and then on the left, of sufficient volume to cause distressing dyspnea. The pleural fluid was aspirated and found to be clear and sterile.

Fig. 2.—Lateral view of the chest taken after injection of an iodized and chlorinated peanut oil into the pericardial sac.

By the end of the fifth postoperative week the temperature rose daily to approximately 100 F., and the pulse rate fluctuated between 100 and 108. The pericardial opening had contracted to about 2 cm. in diameter, and the discharge was seropurulent and small in amount. However, the evidences of circulatory embarrassment became progressively more marked; by the seventh week the abdomen was tense, and edema of the subcutaneous tissues, especially those of the face and chest, was marked. The pulse rate had increased to between 110 and 150, and the volume of the pulse was small. The temperature had risen so that a

maximum daily fluctuation to 101 F. occurred. Serous drainage from the pericardial sac had gradually diminished, and the size of the opening into the sac was now 1 cm. in diameter.

During the eighth week, without any treatment directed to the cardiac condition or the anasarca, a sudden dramatic change occurred. The urinary output increased to a point at which it daily exceeded the intake of fluid by from 1,000 to 1,500 cc. The evidences of toxemia disappeared; the pulse became full and gradually dropped to the normal rate, and the abdominal and pleural fluids vanished. The pericardial discharge by this time had also become small in amount.

Three weeks after the onset of this sudden improvement and seventy days after operation, the patient had recovered sufficiently to walk out of the hospital with the wound healed. Repeated examinations since that time failed to reveal any abnormal cardiac findings, except apparent adherence of the heart to the overlying scar with retraction of the scar at each heart beat. Cardiac reserve appears to be unembarrassed, and the patient has regained his normal weight, with a total increase of 30 pounds (13.6 Kg.), two months after leaving the hospital and five months after his injury.

ELECTROCARDIOGRAPHIC STUDIES

Cole [4] reported apparently the first case of stab wound of the left ventricle with surgical treatment followed by recovery in which electrocardiograms were made. A single tracing (fig. 3 *C*) made six weeks after the injury was practically normal.

In the case reported by Davenport [5] the wound, 5 mm. in diameter, was in the upper portion of the middle third of the right ventricle, 3 mm. from the anterior descending branch of the left coronary artery. The anterior descending branch of the left coronary artery was ligated in the course of the operation (fig. 4 *B*). An inverted T wave persisted in all leads until the fifty-ninth day. Except for a rather low potential, the tracing was normal on the two hundred and fifty-seventh day.

Bates and Talley [6] reported a case of stab wound in the left ventricle. During operation the heart stopped, but cardiac action was restored by massage. A friction rub developed after ten days, and the cardiac shadow was considerably enlarged to the left on the eleventh day but was again normal in size on the twenty-sixth day. The patient was discharged symptom-free twenty-six days after his admission (fig. 5 *A*). A high take-off was recorded for the T wave in leads I and II. The T wave lead III was inverted on the fifth day. By the twentieth day the Pardee curve had been replaced by an inverted T wave in all three leads, which persisted until the ninetieth day. The T wave in lead III was still inverted on the hundred and thirty-second day. The R wave in that lead was irregularly notched in all tracings until, and including, the one taken on the ninetieth day.

4. Cole, D. B.: Ann. Surg. **85**:647, 1921.

5. Davenport, G.: Suture of Wound of the Heart, J. A. M. A. **82**:1840 (June 7) 1924.

6. Bates, W., and Talley, J. E.: Am. Heart J. **5**:232, 1929.

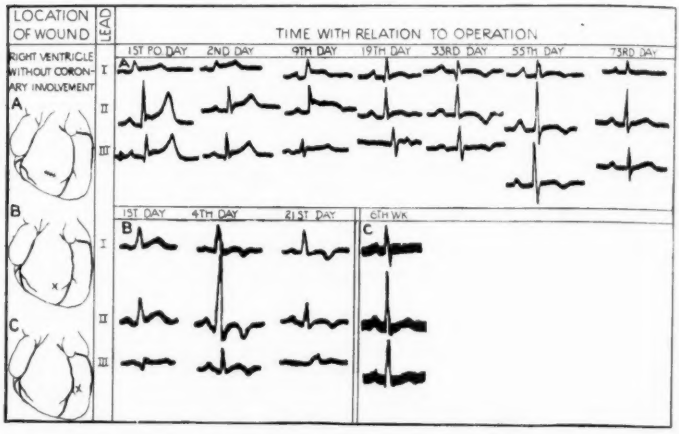

Fig. 3.—Diagrams showing position of the wound and electrocardiograms obtained (*A*) in case 2 of Porter and Bigger (tracings taken from Porter and Bigger [10]); (*B*) in the case of Schlomka (tracings taken from Schlomka [8]), and (*C*), in the case of Cole (tracings taken from Cole [4]).

In this figure and in the following figures, the line with cross-hatching indicates injuries exactly located by the author: ×, those located only approximately.

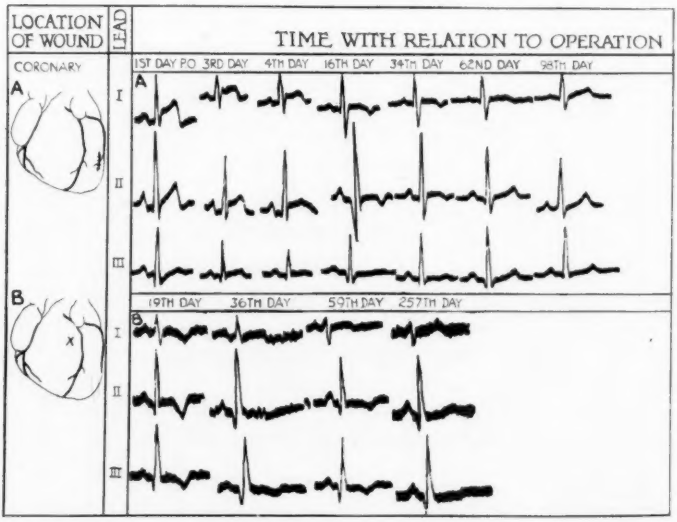

Fig. 4.—Diagrams showing location of the wound and electrocardiograms obtained (*A*) in case 1 of Porter and Bigger (tracings taken from Porter and Bigger [10]) and (*B*) in the case of Davenport (tracings taken from Davenport [5]).

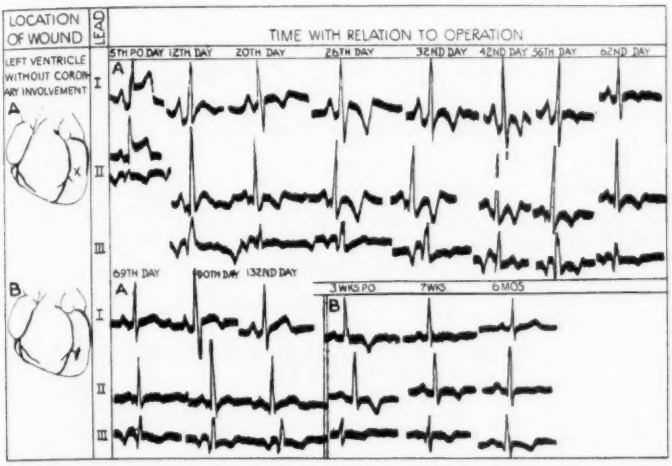
LOCATION OF WOUND
LEAD
TIME WITH RELATION TO OPERATION
LEFT VENTRICLE WITHOUT CORONARY INVOLVEMENT
5TH PO DAY 12TH DAY 20TH DAY 26TH DAY 32ND DAY 42ND DAY 56TH DAY 62ND DAY
69TH DAY 90TH DAY 132ND DAY
3 WKS PO 7 WKS 6 MOS

Fig. 5.—Diagrams showing location of the wound and electrocardiograms obtained (*A*) in the case of Bates and Talley (tracing taken from Bates and Talley [6]) and (*B*) in case 2 of Elkin and Phillips (tracings taken from Elkin and Phillips [7]).

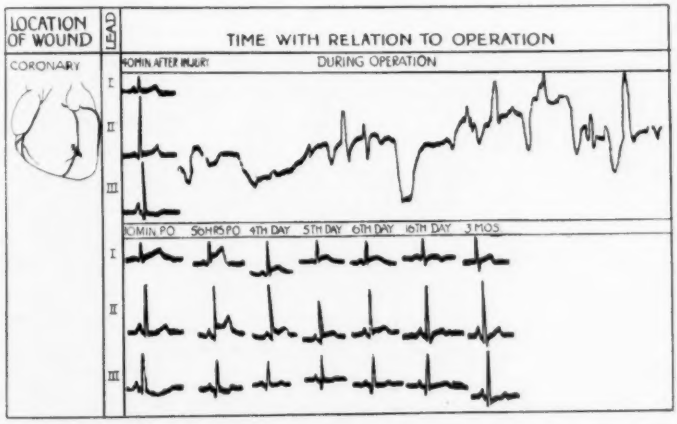
LOCATION OF WOUND
LEAD
TIME WITH RELATION TO OPERATION
CORONARY
40MIN AFTER INJURY
DURING OPERATION
10MIN PO 50HRS PO 4TH DAY 5TH DAY 6TH DAY 16TH DAY 3 MOS

Fig. 6.—Diagram showing location of the wound and electrocardiograms obtained in case 1 of Elkin and Phillips (tracing taken from Elkin and Phillips [7]).

Elkin and Phillips [7] reported two cases in which electrocardiograms were obtained. In the first case the anterior descending branch of the left coronary artery was divided and had to be ligated. Recovery was complete (fig. 6). The first electrocardiogram was made forty minutes after the injury and immediately after operation. It was essentially normal. A tracing made during the operation gave a bizarre QRS complex and nondescript curves. Another tracing made ten minutes after the operation disclosed a slightly elevated take-off in lead I and a depressed take-off in lead III. Fifty-six hours later leads I and II were characterized by a high take-off which, while still elevated, became lower by the fourth postoperative day and disappeared, to be replaced on the sixteenth day by an inverted T wave. Three months after operation the tracings had become normal.

In the second case the stab wound was in the right ventricle and, at the most, involved only a small branch of the descending branch of the left coronary artery (fig. 5 *B*). The first tracing made three weeks postoperatively disclosed an inverted T wave in all the leads. Seven weeks after the operation the T wave was diphasic and in leads II and III was inverted. Six months after operation the only remaining change was an inverted T wave in lead III.

Schlomka [8] reported a case of stab wound on the anterior aspect of the right ventricle without apparent involvement of the coronary arteries (fig. 3 *B*). The electrocardiogram on the first day showed a slight elevation of the take-off, which was replaced on the fourth day by an inversion of the T wave in all leads. This inversion was still present in leads I and II on the twenty-first day. Lead III was of low potential throughout.

Purks [9] included an interesting report of an 18 year old colored youth, who was operated on fifty minutes after being stabbed. The wound had penetrated the right ventricle parallel to the anterior descending branch of the left coronary artery. The artery was cut and had to be ligated. Electrocardiograms (fig. 7) were taken before, during and after operation. The curve obtained before operation displayed a slightly elevated take-off in leads I and II. Tracings made during operation showed bizarre QRS complexes and nondescript curves. Ten minutes after operation the take-off for the T wave in lead I was definitely elevated while that in lead III was depressed. These changes persisted in the tracings with only a gradual diminution in degree until, and including, the one made on the sixth day. On the twelfth day the T wave was diphasic in leads I and II and was inverted in lead III. On

7. Elkin, D. C., and Phillips, H. S.: J. Thoracic Surg. **1**:113, 1931.
8. Schlomka, G.: Deutsche med. Wchnschr. **57**:630, 1931.
9. Purks, W. K.: Am. Heart J. **7**:101, 1931.

the sixteenth day the T wave in leads I and II was diphasic, and on the seventy-sixth day it was inverted in lead I and upright in leads II and III.

Porter and Bigger [10] reported two cases with electrocardiograms. In the first case the wound, 1 cm. in length, was in the left ventricle and divided the posterior descending branch of the left coronary artery. The wound was repaired, and the coronary artery was ligated. The electrocardiogram (fig. 4 *A*) showed a high take-off on the first day which persisted till, and including, the sixth day. It was replaced on the sixteenth day by an inverted T wave which became upright on the sixty-second day.

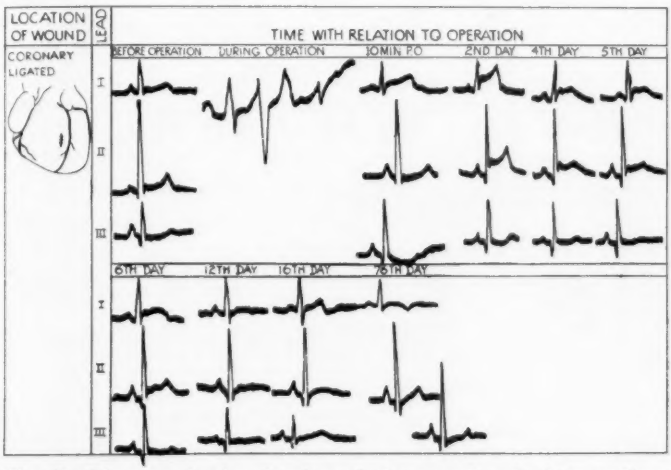

Fig. 7.—Diagram showing location of the wound and electrocardiograms obtained in the case of Purks (tracings taken from Purks [9]).

In the second case the stab wound was in the right ventricle and did not involve the coronary arteries. The electrocardiograms (fig. 3 *A*) were characterized by a low potential in lead I, a large T wave in leads II and III with a high take-off on the first day and a high take-off in all leads on the second day, which persisted through the ninth day. On the nineteenth day the T wave was inverted in leads I and II and was diphasic in lead III. On the thirty-third and fifty-fifth days the T wave was inverted in all leads, and on the seventy-third day, except for a low potential in lead I, the curve was normal.

Both operations were performed with the patients under local anesthesia. Neither pain nor other symptoms were complained of at any

10. Porter, W. B., and Bigger, I. A.: Am. J. M. Sc. **184**:799, 1932.

time in either case. The authors in discussing this point explained the absence of pain on the basis of the loss of muscular contractions due to the severance of the muscle fibers, and they emphasized the factor of muscular work in the explanation of pain from occlusion of the coronary arteries. In support of this theory they referred to the case of Burian,[11] in which a branch of the coronary artery was divided with only superficial injury to the muscle. The vessel was ligated. Postoperatively, anginal pain was a troublesome symptom.

Schmidt-Weyland[12] reported a case of attempted suicide occurring in 1895 in which the heart was wounded by a bullet from a pistol. Surgical repair was made. In 1907 the patient complained of an occasional sense of pressure and stabbing pain in the region of the heart. The lips were slightly cyanotic; the pulse rate at that time was 48. In 1930 the patient had no cyanosis. The heart was of normal size; the blood pressure was 170 systolic and 70 diastolic. The patient had a total heart block, and the electrocardiograms, which were not reproduced in the report, were described as follows: T wave diphasic in leads I and II; P wave diphasic in all leads.

Baledent and Bizard[13] reported a case in which extrasystoles occurred at long intervals after a stab wound of the heart immediately below the auriculoventricular ring in the left ventricle. The electrocardiograms showed a right ventricular extrasystole in leads I and II, which the authors regarded as possibly septal in origin.

Ramsdell[14] reported a case of symptomatic recovery but with a persistently inverted T wave after five months.

ELECTROCARDIOGRAPHIC FINDINGS IN OUR CASE

Electrocardiograms in our case (fig. 8) disclosed a high take-off of the T wave (Pardee curve) in both the first and the second lead with low voltage in all leads on the day after operation. By the fifth day the take-off was still elevated, although not as high as before, and lead III, which on the first day was almost iso-electric, displayed a higher voltage with an inverted T wave.

On the ninth day the high take-off was still present in the first and second leads; the T wave was upright in the third lead; on the fifteenth day the take-off was only slightly elevated with the convexity upward to an inverted T in leads I and II, and the T wave in lead III was iso-electric.

---

11. Burian, F.: Casop. lék. česk. **61**:585, 1922.
12. Schmidt-Weyland, P.: Deutsche med. Wchnschr. **57**:2014, 1931.
13. Baledent, M., and Bizard, G.: Compt. rend. Soc. de biol. **103**:730, 1930.
14. Ramsdell, E. G.: Ann. Surg. **49**:141, 1934.

On the twenty-fifth day a well marked inversion of the T wave was present in all three leads and still persisted on the forty-fourth day.

Five months after operation the electrocardiogram was entirely normal in all three leads.

The electrocardiograms in the cases already cited were copied and arranged according to the site of injury (figs. 3 to 8). The electrocardiographic tracings obtained showed no relation either to the location of the injury or to ligation of the coronary arteries. We must add, however, that in each case the wound was on the anterior surface of either the right or the left ventricle. In Purk's case an electrocardiogram obtained before operation disclosed a slight elevation of the take-off for the T wave in leads I and II, while the electrocardiogram made before operation in case 1 reported by Elkin and Phillips [7] showed practically no change from the normal tracing. Both these authors obtained

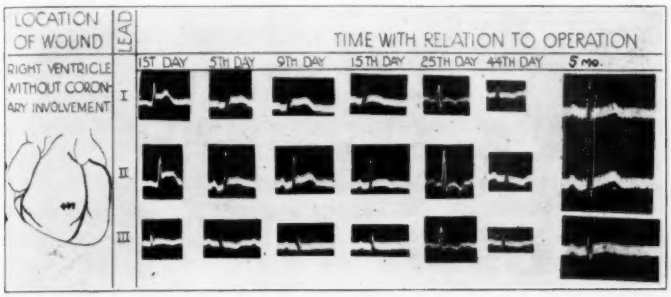

Fig. 8.—Diagram showing location of the wound and electrocardiograms taken in our case.

a tracing during operation showing irregular and bizarre QRS waves. Tracings made a few minutes postoperatively in these cases disclosed an elevated take-off for the T wave in lead I and a concave take-off to an inverted T wave in lead III. A high take-off developed and persisted until from the fourth to the sixth day in all of the cases reported, except in case 2 of Porter and Bigger, in which it persisted until the ninth day, and in Schlomka's case, in which it had disappeared from the tracing on the fourth day. Since in most of the tracings an interval of from six to ten days occurred between the last tracing showing a Pardee curve and the first one in which it was absent, one may assume that it persists for from about four to ten days postoperatively. It is uniformly replaced by an inverted T wave which in some instances (Purk's case on the sixteenth day) goes through a diphasic stage. This stage persists for a variable period of from about four to twelve weeks. A low potential (Porter and Bigger [case 2] and Davenport) and a

notched R wave in lead III (Bates and Talley) occurred but were not constant. A return to a normal curve apparently occurs ultimately in the vast majority of cases.

POLYSEROSITIS (PICK'S SYNDROME)

The development and sudden disappearance of the anasarca in this case merits further consideration. Pool [15] discussed the treatment of purulent pericarditis and reported the occurrence of abdominal distention and generalized edema after irrigation of the pericardial sac with surgical solution of chlorinated soda for ten days. The irrigations were discontinued because the amount of discharge had become small. The generalized anasarca disappeared in two weeks. Other authors cited by Pool reported no ill effects from the same procedure.

Beck [3a] injected surgical solution of chlorinated soda into the normal pericardial sac of dogs and found that it caused pain and bleeding. The pulse rate usually increased promptly after the solution was introduced. Within a few weeks pericarditis, with either effusion or adhesions, resulted. Generalized edema and polyserositis occurred in a few instances.

Subsequently, Beck and Griswold [3b] reported results obtained in a larger series of dogs. Surgical solution of chlorinated soda was injected into the pericardial sac, and a rise in venous pressure, polyserositis and, finally, edema resulted in some of the animals. The authors concluded that Pick's syndrome is due essentially to the inability of the heart to fill because of the diminished capacity of the pericardial sac. Pericardiectomy when instituted sufficiently early resulted in recovery, an observation partially verified in one patient.

Cox [16] reported two cases of wounds of the heart. In the second case generalized anasarca and dyspnea developed rather acutely on about the thirty-seventh postoperative day. Forty-six days later, after treatment with digitalis and merbaphen, the patient recovered. One year later there was no evidence of cardiac insufficiency.

PERICARDITIS AND POLYSEROSITIS IN OUR CASE

Pericarditis developed in our case, and the pericardial sac was opened widely. Irrigations with surgical solution of chlorinated soda were begun and continued at decreasing intervals for eighteen days. Many of the irrigations were accompanied by thoracic and abdominal pain and were followed within an hour by nausea and occasionally by vomiting. On the twenty-eighth postoperative day an iodized and chlorinated peanut oil was injected into the pericardial sac, and roentgenograms were

15. Pool, E. H.: Ann. Surg. **73**:393, 1921.
16. Cox, D. M.: Wounds of the Heart, Arch. Surg. **17**:484 (Sept.) 1928.

made (figs. 1 and 2). The opaque medium was irregularly distributed in pools and scattered irregularly in thin layers over the surface of the heart. The sac was not obliterated at this time. On the twenty-ninth postoperative day physiologic solution of sodium chloride was substituted for surgical solution of chlorinated soda as the irrigating fluid. On the thirtieth postoperative day ascites, and within a few days generalized anasarca and hydrothorax, were found on physical and roentgen examination.

Without specific therapy either for the edema or for the cardiac condition, a spontaneous, rapidly increasing urinary output began five weeks after the onset of these symptoms. Simultaneously, the evidences of polyserositis diminished, and symptomatic improvement progressed uneventfully, so that the patient was able to leave the hospital ten weeks after his admission and seven weeks after the onset of ascites, free from symptoms. He is symptom-free at the time of writing.

PROGNOSIS AND COMPLICATIONS

Stewart [17] reported subsequent observations in three cases of wounds of the heart. In the first case a 20 year old Negro suffered severe pain and dypsnea at the time of receiving the wound and in the hospital. The left lung was collapsed, and the anterior wall of the left ventricle was wounded. The coronary artery was wounded during operation and had to be ligated. Four years later (1908) the patient was symptom-free. Tuberculous inguinal adenitis occurred in the interim, and the patient died five years after injury (1909) from pulmonary tuberculosis. At autopsy obliterative pericarditis was observed. The heart weighed 370 Gm., and the old scar in the right ventricle was recognized. In the second case the patient was symptom-free after four years, and in case 3 the patient, seen two years after injury, did not complain of symptoms.

Hesse,[18] in an exhaustive summary and analysis of one hundred and nineteen cases of wounds of the heart (twelve from his own hospital) in which the patients survived operation, concluded that in 77.3 per cent of the instances complete restitution of function was obtained and that in 22.7 per cent fair results and in 1.7 per cent poor results were seen. One patient died as a result of the pathologic condition, but only after complete recovery from the wound, and the author considered that the adhesive pericarditis which generally appears after operative intervention is the primary cause of the dysfunction that may occur. In the series of cases in which recovery took place, persons experienced attacks of pneumonia, measles, grip, etc., during epidemics, hard work, war,

17. Stewart, F. T.: Ann. Surg. **58**:67, 1913.
18. Hesse, E.: Deutsche Ztschr. f. Chir. **190**:239, 1925.

a hobo existence and a state of chronic alcoholism without apparent cardiac symptoms. The author emphasized the fact that ligature of the descending branch of the left coronary artery and its branches does not influence the end-results. The end-results are somewhat poorer in cases that are complicated by purulent pericarditis, but even in these instances complete recovery is not uncommon and the working capacity is frequently large. Adhesive pericarditis and mediastinopericarditis resulted in two cases with ultimate death from cardiac insufficiency.

Urrutice and Zamora [19] reported an instance of stab wound of the heart in a 19 year old man, who complained of precordial pain one month after operation, and when seen two years later, still complained of precordial pain and dyspnea.

Jones [20] reported a case in which a stab wound of the left ventricle was sutured, presumably without anesthesia as the patient was unconscious when operated on. Six months later the patient complained of occasional moderate precordial pain and dyspnea on exertion, and the heart rhythm was disturbed.

Brunetti [21] reported a case of aneurysm near the apex of the left ventricle resulting from a stab wound of the heart.

Rufanov [22] reported the result of suture of a stab wound of the heart after twenty-eight years, performed with the patient under chloroform anesthesia. No ill effects, in the form either of pain or of impairment of cardiac efficiency, were noted.

COMMENT

From the standpoint of electrocardiographic changes resulting from wounds on the anterior surface of the heart, the picture varies but little from case to case, regardless of the presence or absence of involvement of the large coronary vessels or of the region of the anterior surface of the ventricle damaged. The primary change is a rise in the take-off of the T wave with a gradual return to the iso-electric line, accompanied by inversion of the T wave within ten days. In the vast majority of cases the final complete return of a normal curve is observed. One is forced to conclude that the electrocardiographic changes noted are, as is the generally accepted opinion, purely myocardial in origin and are dependent on the degenerative changes that occur in the muscle fibers involved.

The rarity of pain at the time of injury or subsequent to it, as well as the complete absence of pain during operation in the cases in which

19. Urrutice, C., and Zamora, M. A.: Bol. de cir. de Chile **10**:350, 1932.
20. Jones, J. F.: Ann. Surg. **65**:120, 1917.
21. Brunetti, L.: Riv. d. radiol. e fis. med. **4**:669, 1932.
22. Rufanov, I. G.: Zentralbl. f. Chir. **58**:3138, 1931.

only local anesthesia was used, supports the theory that the pain of cardiac origin is due to changes occurring only in the presence of intact muscle. It might be explained as being due to stretching of the cardiac muscle fibers or, in other words, to local dilatation of the myocardium. The possibility that anoxemia of the muscle fibers causes the pain cannot be discarded. The actively functioning intact muscle presumably becomes anoxemic sooner than the divided muscle under similar circumstances.

Recently, Pickering and Hess,[23] in their work on the mechanism of headache, concluded that the sensory fibers of the meninges are located in the perivascular tissues and are affected by vascular tension. The possibility that a similar mechanism is present in the heart should be investigated.

With regard to the polyserositis which complicated our case, apparently as a result of the use of surgical solution of chlorinated soda or of the infection or of both, several points should be emphasized. If mere scarring of the pericardial sac were the only factor, spontaneous recovery would have to be explained by stretching of the scar tissue. Scar tissue tends to contract, and therefore one would expect a recurrence of the syndrome at some future time.

One year after the injury in Cox' case and five months after operation in our case there has been no recurrence of symptoms. The inflammation per se might induce these changes by direct reflex effect. Furthermore, the roentgenograms made after injecting an iodized and chlorinated peanut oil into the pericardial sac only two days prior to the onset of the clinical symptoms disclosed only moderate obliteration of the sac, with but little involvement about the base of the heart.

The reduction of pericardial capacity may have resulted from encroachment on the space by loculated or excessively thick exudate or by local edema. Such processes would have resolved in the course of healing of the inflammation, thus accounting for the return of adequate pericardial capacity.

However, this mechanical conception of the pathogenesis of polyserositis fails to explain the occurrence of encapsulated fluid in the right pleural cavity in our case and the usual observation of proliferative inflammation of the capsules of the liver and spleen seen at autopsy in this condition. The inflammatory reaction, though primary in the pericardial sac, also develops in other serous membranes. This might come about by lymphatic dissemination of bacteria, bacterial toxins or a chemical such as surgical solution of chlorinated soda. The primary lesion in the pericardium then becomes a focus from which the inflammatory agent, whether bacterial, toxic or chemical, is disseminated to the other serous membranes with the resultant serositis involving the

23. Pickering, G. W., and Hess, W.: Clin. Sc. **1**:77, 1933.

pleura and abdominal membranes. The localization of the peritoneal involvement in the upper part of the abdomen, i. e., in the capsule of the liver and spleen, speaks strongly in favor of this view. The general subcutaneous anasarca, especially pronounced in the head, neck, upper extremities and chest, must be explained by venous obstruction.

These points can be settled only by further careful experimental observations along the lines of the experiments reported by Beck.

Finally, the circumstances under which the operation was performed with complete recovery serve to emphasize the fact that cardiac tamponade is a condition of extreme emergency. Whether it would have been better to aspirate the pericardial sac in this case, thus decompressing the sac and perhaps allowing more time for preoperative preparation, is problematic. At any rate, it is apparent that even with the heart at complete standstill the life of the patient may still be saved. And with this primary purpose in mind, sterility and the possibility of subsequent postoperative complications have to be disregarded.

SUMMARY

A case of stab wound of the heart with recovery is reported.

Complete electrocardiographic studies and their comparison with similar studies show that a Pardee curve, replaced after about ten days by an inversion of the T wave, occurred in all cases. A complete return to the normal curve is the rule.

Our case was complicated by polyserositis, which may have resulted from the use of surgical solution of chlorinated soda in irrigating the pericardial sac after the development of pericarditis. The mechanism of the development of polyserositis is discussed.

Roentgenographic visualization of the pericardial sac after injection of an iodized and chlorinated peanut oil was carried out. The pictures disclosed little obliteration of the pericardial sac.

The operation performed without anesthesia or anything more than the most cursory attempts at sterility, necessitated by the extreme state of the patient, resulted in ultimate and complete recovery.

INFECTION AND HEMORRHAGIC NEPHRITIS

WALTER L. WINKENWERDER, M.D.
NEIL McLEOD, M.D.
AND
MYLES BAKER, M.D.
BALTIMORE

Infection as a cause of diffuse hemorrhagic or glomerular nephritis is well known. Since Loehlein's [1] (1907) and Fahr's [2] (1912) fundamental observations emphasizing the frequency with which glomerular nephritis is associated with streptococcic infections, usually of the upper respiratory tract, subsequent extensive studies,[3] both clinical and experimental, have tended to confirm these observations.

Longcope and his associates [4] (1927) published the results of detailed clinical and bacteriologic studies of forty cases of acute and subacute glomerular nephritis. The onset of an overwhelming majority of the cases in their series (85 per cent) was accompanied or preceded by acute infections of the upper respiratory tract, of which 68.7 per cent showed the beta type, and 12.2 per cent the alpha type, of the hemolytic streptococcus. After years of observation they concluded that disappearance of infection and of the hemolytic streptococcus was related to recovery in nephritis and, contrariwise, that persistence of

---

This study was aided by a grant from the Ella Sachs Plotz Foundation.

From the Medical Clinic, School of Medicine, Johns Hopkins University and Hospital.

1. Loehlein, M.: Ueber die entzündlichen Veränderungen der Glomeruli menschlichen Nieren und ihre Bedeutung für die Nephritis, Leipzig, S. Hirzel, 1907 (forms pt. 4 of Arb. a. d. path. Inst. zu Leipzig, 1907); Ueber Nephritis nach dem heutigen Stande der pathologisch-anatomischen Forschung, Ergebn. d. inn. Med. u. Kinderh. **5**:411, 1910.

2. Fahr, T. Z.: Können wir die Nierenkrankungen nach ätiologischen Gesichtspunkten einteilen? Virchows Arch. f. path. Anat. **220**:277, 1912.

3. Bell, E. T.; Clawson, B. J., and Hartzell, T. B.: Experimental Glomerular Nephritis, Am. J. Path. **1**:247, 1925. Kollert, V.; Suchanek, E., and Singer, S.: Grundlagen der ätiologischen Behandlung der Nierenentzündungen, Leipzig, Franz Deuticke, 1929. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930. Munk, F.: Die Nierenkrankheiten, ed. 2, Berlin, Urban & Schwarzenberg, 1925. Gray, J.: Causes and Sequences in Nephritis, J. Path. & Bact. **31**:191, 1928. Lichtwitz, L.: Praxis der Nierenkrankheiten, Berlin, Julius Springer, 1925. Van Slyke, D. D.; Stillman, E.; Moller, E.; Ehrich, W.; McIntosh, J. F.; Leiter, L.; MacKay, E. M.; Hannon, R. R.; Moore, N. S., and Johnston, C.: Observations on the Courses of Different Types of Bright's Disease and on the Resultant Changes in the Renal Anatomy, Medicine **9**:257, 1930.

4. Longcope, W. T.; O'Brien, D. P.; McGuire, J.; Hansen, O. C., and Denny, E. R.: Relationship of Acute Infections to Glomerular Nephritis, J. Clin. Investigation **5**:7, 1927.

infection and of the streptococcus was related in some way to progression of the disease.

Our purpose in the present communication is to report in detail an analysis of the various relationships between infection by Streptococcus haemolyticus and hemorrhagic nephritis. The data presented are based on a study of seventy-eight cases of hemorrhagic nephritis made by Dr. Longcope and a group of his associates over a period of nine years (including the series reported in 1927). For convenience in the presentation of the material the seventy-eight cases have been divided into three groups according to the status of the disease: group 1, hereafter termed the "well group," cases in which no evidence of the condition remains; group 2, hereafter termed the "latent group," cases in which it is latent; group 3, hereafter termed the "progressive and fatal group," cases in which it is progressive and chronic and those in which it has terminated fatally. A chart of each group illustrates the entire course of the disease in each patient. The essential criteria making this division possible were based on the correlated results of all the methods of study mentioned in subsequent sections of this paper. The proper status of the majority of the cases has undoubtedly been determined, but in several instances, especially in the latent group, a reshuffling may eventually be necessary, since in several of the cases which have been followed for a year or less the patients may become well or, on the contrary, their condition may progress imperceptibly to a chronic stage With few exceptions, the patients classsified (according to the criteria of Addis [5]) as either well or in the latent phases of nephritis were seen within a few days to a few weeks after the apparent onset of their disease, while a few acquired the disease while they were under observation. On the other hand, several of the patients whose nephritis was in the progressive stage or had terminated fatally were seen months and sometimes years after the alleged onset. Periodically, also, the majority of the patients were readmitted to the hospital for completion of various tests of renal function, including the dilution and concentration test of Volhard,[6] the phenolsulphonphthalein test, the urea clearance test of Van Slyke [7] and the quantitative estimation of the formed elements in the urine as described by Addis.[8] The accessory nasal sinuses were always examined, and operative procedures were performed by Dr. Crowe and his staff.

5. Addis, T.: A Clinical Classification of Bright's Disease, J. A. M. A. **85**:163 (July 18) 1925.

6. Volhard, F., in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1931, vol. 6.

7. Moller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: Relation Between Urine Volume and Rate of Urea Excretion by Patients with Bright's Disease, J. Clin. Investigation **6**:485, 1928.

8. Addis, T.: The Number of Formed Elements in the Urinary Sediment of Normal Individuals, J. Clin. Investigation **2**:409, 1925.

FORMS OF INFECTION OBSERVED AT THE ONSET OF HEMORRHAGIC OR GLOMERULAR NEPHRITIS

The various forms of infection noted at the onset of nephritis are shown in table 1. Infections of the upper respiratory tract comprised 67.6 per cent of the total number, with tonsillitis the most frequent by far (44 per cent). With the exception of the small number (two) of cases of scarlatinal nephritis in this series, the frequency of infections of the upper respiratory tract agreed in general with data presented on other large series of cases of glomerular nephritis, and only a few of the other infections justify further comment.

Bronchitis was noted in six cases (1, 20, 21, 22, 38 and 57). In two of these cases (1 and 57) infection of the upper respiratory tract

TABLE 1.—*Forms of Infection Observed at the Onset of Seventy-Seven Cases of Hemorrhagic Nephritis, and the Frequency of Each in the Series*

Form of Infection	Frequency	Percentage
Tonsillitis and pharyngitis	41	44
Sinusitis	14	15
Pharyngitis	8	8.6
Bronchitis	6	6.5
Pneumonia	6	6.5
Scarlet fever	2	2.1
Abscess	2	2.1
Typhoid fever	1	1.1
Erythema	1	1.1
Subacute bacterial endocarditis	1	1.1
Rheumatic fever	4	4.3
Otitis media	1	1.1
Latent syphilis	6	6.5
Total	92	100

was not observed; in the other four the bronchitis was associated with, and undoubtedly was secondary to, tonsillitis, sinusitis or pharyngitis.

Pneumonia was observed in six cases (13, 15, 46, 51, 72 and 78). Patients 72 and 78 came under observation several months after the onset of their nephritis and therefore were inappropriate for analysis. Considerable doubt has recently been thrown on the previously accepted occurrence of hemorrhagic nephritis in pneumococcic pneumonia; hence the determination of the etiology of the pneumonia in the remaining four cases was important. Although Blackman, Brown, and Rake[9] produced the pathologic changes characteristic of acute and subacute nephritis in rabbits by intravenous injections of an autolysate prepared from Pneumococcus, type I, as well as by intradermal injections of virulent strains of the same organism, postmortem investigation

9. Blackman, S. S.; Brown, J. H., and Rake, G.: The Production of Acute Nephritis by Means of a Pneumococcal Autolysate, Bull. Johns Hopkins Hosp. **48**:74, 1931.

by Blackman and Rake [10] in human beings revealed that apparently the occurrence of acute glomerular nephritis is limited to infants suffering from chronic pneumococcic infection, such as empyema, organizing pneumonia or pericarditis. In older children or adults no such changes were observed. Furthermore, in thirty-two cases of lobar pneumonia, also studied pathologically, not a single instance of diffuse nephritis was found. MacCallum,[11] Aschoff [12] and Fahr [13] have referred to the development of acute nephritis in lobar pneumonia. None of the four cases of pneumonia in this series could be definitely attributed to the pneumococcus, as the following brief abstracts indicate:

CASE 13.—The patient had chronic tonsillitis, bronchopneumonia and nephritis on admission to the hospital. Hemolytic streptococcus, beta type, was cultured from both the sputum and the pharynx. Pneumococci were never found.

CASE 15.—The patient had a chronic cough for three weeks. On admission there was consolidation of the upper right lobe, chronic tonsillitis, chronic rheumatic endocarditis (apparently quiescent) and hemorrhagic nephritis. No sputum was ever obtained for culture; the pneumococcus was not found in cultures from the throat. Cultures of the blood were negative. Hemolytic streptococcus, beta type, was grown from the surface of the tonsils and from the ground-up tonsils after tonsillectomy.

CASE 46.—The patient was comatose on admission to the hospital following repeated generalized convulsions of several days' duration. There were marked anasarca, oliguria and nitrogen retention. Death occurred before adequate examination or cultures of the throat were made. Postmortem examination revealed acute sinusitis and lobular pneumonia; Staphylococcus aureus was grown from the former, but Str. hemolyticus, beta type, from the lungs; pneumococci were never found.

CASE 51.—The patient had three attacks of rheumatic fever prior to admission, the last beginning eight days before admission. Edema appeared two days before admission, when the patient presented chronic rheumatic endocarditis, hypertension, great anasarca, pronounced anemia, bronchopneumonia of the right lower lobe and urinary sediment characteristic of severe nephritis. Pneumococcus, type II, and Str. haemolyticus, beta type, were cultured from the sputum; this streptococcus was also obtained repeatedly from the tonsils and pharynx. The presence of both organisms prevented assigning definite etiologic significance to either.

The striking rarity of infections other than those of the respiratory tract was so evident that little comment seems necessary. It is interesting, however, that acute nephritis of rather severe form developed during

10. Blackman, S. S., and Rake, G.: Acute Pneumococcal Nephritis, Bull. Johns Hopkins Hosp. **51**:217, 1932.

11. MacCallum, W. G.: A Textbook of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 267.

12. Aschoff, Ludwig: Pathologische Anatomie, ed. 4, Jena, Gustav Fischer, 1919, p. 521.

13. Fahr, Theodore, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 5, pt. 2, p. 285.

the course of typhoid fever in one patient (case 33), who is now in the latent phase of the disease. Heavy albuminuria and cylindruria characterized the urinary sediment; only an occasional red blood cell was found. The ultimate clinical course excluded the possibility of pyelitis as a cause of the urinary changes. Chronic tonsillitis coexisted, however, and hemolytic streptococci, beta type, were grown in small numbers; following an exacerbation of the tonsillar infection they grew abundantly. Whether the nephritis was caused by the streptococcic or by the typhoid infection is uncertain; but in view of the character of the urinary abnormalities it seems possible that the nephritis in this case was produced by the typhoid fever.

In view of the recent statement of Coburn [14] and many others that Str. haemolyticus is related etiologically to rheumatic fever, the association of rheumatic fever with only four cases of hemorrhagic nephritis in this series is highly interesting. Goldring,[15] employing the technic of Addis, showed that the urine in many cases of acute rheumatic fever contained abnormally large numbers of red blood cells; in pneumonia and myocardial insufficiency, no such changes were noted. The association of acute hemorrhagic nephritis with acute rheumatic fever was noted and described by Goldring,[16] Loeb [17] and Coburn.[18] The latter attributed the urinary changes, which simulated ordinary acute nephritis, to hemorrhage in common with other hemorrhagic phenomena, such as epistaxis and purpura, which occur during what he termed "the third phase in the evolution of the rheumatic process." The urinary sediment is characterized chiefly by hematuria and minimal cylindruria, although one of Goldring's and one of Loeb's patients exhibited large amounts of albumin. Pronounced renal insufficiency may supervene. If the view that Str. haemolyticus is responsible for rheumatic fever and also for hemorrhagic nephritis is true, it is curious that despite the close and not infrequent association of what appears to be hemorrhagic nephritis with acute rheumatic fever the antithesis, or development of rheumatic fever during the course of acute diffuse nephritis, as presented here, did not occur in this series. Only in case 51 did it appear

14. Coburn, Alvin F., and Pauli, R. H.: Studies on Relationship of the Streptococcus Haemolyticus to the Rheumatic Process, J. Exper. Med. **56**:609, 1932.

15. Goldring, W., and Wyckoff, J.: Studies of the Kidney in Acute Infections: Observations with the Urine Sediment Count (Addis) in Acute Rheumatic Fever, J. Clin. Investigation **8**:569, 1930.

16. Goldring, W.: Occurrence of Diffuse Glomerulonephritis in Acute Rheumatic Fever, M. Clin. North America **14**:1551, 1931.

17. Loeb, R. F.: Unusual Manifestations of Rheumatic Fever in Relation to Newer Concepts of This Disease, M. Clin. North America **4**:1540, 1931.

18. Coburn, Alvin F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues, Am. J. Dis. Child. **45**:933 (May) 1933.

likely that nephritis developed during an exacerbation of the rheumatic process. No definite rheumatic manifestations other than quiescent endocardial lesions were noted at the onset of the nephritis in the other three cases, notwithstanding the fact that infections of the upper respiratory tract associated with hemolytic streptococci, beta type, had occurred.

INCIDENCE OF STR. HAEMOLYTICUS IN HEMORRHAGIC NEPHRITIS

The bacteriologic studies presented here regarding the incidence of Str. haemolyticus in the infections associated with hemorrhagic nephritis represent, with few exceptions, the results of cultures made as soon as observations were begun and periodically thereafter throughout the course of the disease. If a causal relationship between infections due to the hemolytic streptococcus and nephritis is presumed, the evidence desirable and, indeed, necessary to strengthen this presumption must be derived from bacteriologic observations made not only at the onset

TABLE 2.—*Incidence of Hemolytic Streptococcus in Seventy-Eight Cases of Hemorrhagic Nephritis*

Type of Organism	Well Group	Latent Group	Progressive and Fatal Group	Total
Beta	21	17	24	62
Alpha	0	0	5	5
No organisms	1	3	7	11

but also during the later phases of the disease. The organism should be present during the initial stages or during the chronic stages of the disease, if the latter develop; and, contrariwise, if the patient recovers from nephritis, it is reasonable to assume that the hemolytic streptococci should disappear.

The majority of the patients who recovered or in whom the condition became latent came under observation during the acute or active stage of infection, and cultures were obtained periodically, in most instances, in these two groups throughout the entire course of the disease. In contrast, in the group in which the disease proved progressive or fatal, several patients presented themselves weeks, months and occasionally years after the onset. Bacteriologic data on the latter group are nevertheless of importance, since owing to the assiduity with which focal infection was attacked when the condition of the patient permitted, chronic infection in the well group and the group in which the disease became latent proved relatively infrequent. The cultural findings, therefore, though not comparable in the three groups, are complementary.

Table 2 illustrates the incidence of the hemolytic streptococcus in the three groups of cases, irrespective of the stage of nephritis. Sixty-seven cases, or 92 per cent, showed the beta type; five, or 8 per cent, all

progressive or fatal, showed the alpha type (alpha prime). The beta type was recovered on only two occasions in these five cases, but in such small numbers as to be considered of relative unimportance. In eleven cases, designated as showing "no organisms" in charts 1, 2 and 3, neither type of the streptococcus was obtained.

Table 3 illustrates further the incidence of Str. haemolyticus in the active or initial phase of nephritis, compared with the incidence when it became eventually possible, in the course of the disease, to divide the entire series into the three groups: well, latent, and progressive or fatal. The point of interest in the table is the high percentage of positive cultures obtained during the active stage in the well and latent groups as compared with the sharp decrease in positive cultures when the

TABLE 3.—*Incidence of Hemolytic Streptococcus During Successive Stages of Nephritis*

	Active Stage			Well, Latent and Progressive Stage		
Group	Str. Haemolyticus	Incidence	Percentage	Str. Haemolyticus	Incidence	Percentage
Well group.....	+	20	90	+	7	32
(22 cases)	0	2	10	0	15	68
Latent group.....	+	16	80	+	6	32
(20 cases)	0	4	20	0	13	68
				No culture	1	4.9
Progressive and fatal group...	+	19	73	+	19	63.3
(36 cases)	0	7	27	0	11	36.6
	No culture	10		Patient died in acute stage	6	

patients either recovered or entered the latent phase. Of these groups, 90 and 80 per cent, respectively, gave positive cultures during the active stage, but eventually organisms were no longer obtained in 68 per cent of both groups. In the group with progressive nephritis or dead, however, the incidence maintained a tenacious constancy: Seventy-three per cent gave positive cultures during the initial stage and 63 per cent during the progressive stage. Cultures were taken from twenty-six patients in the initial stage of nephritis: Nineteen gave positive cultures, and of these, six died during the early weeks of the disease, nine continued to harbor the organism during the chronic active stage and only four reverted to a negative state. Seven patients of this group gave consistently negative cultures throughout the entire course of their disease. Ten additional ones came under observation after the initial phase of the disease had passed, but cultures were positive and continued so throughout the period of observation. It is interesting to note that the five cases classified as due to streptococcic infections, alpha type, were all confined to the progressive group.

From the foregoing data one may conclude, therefore, that Str. haemolyticus is apparently related to successive phases of hemorrhagic nephritis, since this organism was recovered from the great majority of the patients in the active phase of the disease, and disappearance of this organism occurred in the majority of those who recovered or in whom the disease subsided to the latent stage, whereas persistence of the streptococcus was characteristic of the chronic stage of the disease. This relationship was established and emphasized by Longcope,[4] and this analysis merely confirms his views.

THE CHARACTER OF INFECTIONS OBSERVED AT THE ONSET OF NEPHRITIS

An attempt to judge quantitatively the intensity of infections observed at the onset of nephritis is obviously difficult. This was especially true of many cases in this series, some of which were seen when

TABLE 4.—*Character of Infections Observed at Onset of Seventy-Seven Cases of Hemorrhagic Nephritis*

Character of Infections	Well Group (22 Cases)	Latent Group (20 Cases)	Progressive and Fatal Group (35 Cases)	Total
Acute	19 (85%)	19 (95.2%)	9 (25%)	47
Chronic	3 (15%)	1 (48%)	17 (50%)	21
No demonstrable infection	0	0	9 (25%)	9

the manifestations of acute infection were subsiding, or when, comparatively late in the disease, the evidence of chronic infection was questionable or seemed insignificant; in fact, in several cases infection was never demonstrated. However, differentiation between acute and chronic infection, irrespective of the factor of intensity, was possible, and in attempting the classification of the cases on this basis, as shown in table 4, two outstanding relationships were found.

Acute infection accompanied by definite constitutional symptoms occurred in forty-seven cases, or 61 per cent of the entire series. Of these, thirty-eight, or 80 per cent, were equally divided between the well and latent groups; only nine, or 20 per cent, were in the chronic or fatal group. In this series, therefore, hemorrhagic nephritis the onset of which was preceded or accompanied by acute infection with definite constitutional symptoms almost invariably pursued a favorable course. This observation suggests the presence of modifying factors other than the initial infection precipitating the nephritis which, preventing recovery, might have caused progression of the disease or death of the patient in the nine cases mentioned (44, 45, 51, 56, 57, 62, 69, 72 and 75). Detailed analysis of the records disclosed that such factors, namely, intercurrent infections, undoubtedly were the primary cause of

death in three fatal cases and of progressive nephritis in three other cases, as the following brief abstracts illustrate.

CASE 44.—The patient had severe hyperthyroidism of sixteen months' duration. Acute tonsillitis and pharyngitis developed while he was in the ward, followed in sixteen days by acute hemorrhagic nephritis. In the second week of the latter illness, accidental varicella infection was contracted, and death followed quickly.

CASE 45.—The patient had acute pharyngitis complicated by cervical adenitis and hemorrhagic nephritis. Drainage of the involved cervical glands revealed the presence of the hemolytic streptococcus, beta type. There was rapid development of multilobar pneumonia with bacteremia, caused by Pneumococcus, type IV; 15 colonies per cubic centimeter were counted in blood culture. The patient died on the fifth day of the latter infection.

CASE 51.—This case has already been abstracted (p. 300). Nephritis apparently occurred during the sixth day of an exacerbation of rheumatic fever. Pneumonia developed during the active stage of the nephritis; the latter became progressive without an intervening latent phase, and death followed in seven months.

CASES 56, 57 and 75.—The patients had recurring infections associated with severe exacerbations of nephritis which ushered in the progressive stage of nephritis.

In cases 44, 45 and 51, death was due, undoubtedly, to a combination of infections; it could not be attributed primarily to nephritis. In cases 56, 57 and 75, intercurrent infections probably caused progression of the nephritis. Only three cases (62, 69 and 72), then, in which nephritis followed severe acute infection became chronic for reasons not recognized.

In striking contrast to the favorable progress of hemorrhagic nephritis in which the onset was associated with acute infection accompanied by constitutional symptoms was the course of nephritis with which there was either chronic infection or, in some cases (nine), no demonstrable infection at all. Thirty cases, or 40 per cent of the series, belonged in this category; of these, twenty-six cases, or 85 per cent, were progressive or fatal; only three, or 10 per cent, resulted in recovery, and only one became latent. Some question arose as to the proper classification of these cases, seventeen of which were allocated to the "chronic infection" group, and nine to the "no infection" group (charts 1, 2 and 3, and table 4). All the patients denied having any symptoms or manifestations of acute infection at or directly preceding the onset of nephritis, and in five patients no infection was ever demonstrated while they were under observation. Some, however, came under observation months, or, in a few instances, years after the alleged onset of their disease, and on this basis one may justifiably doubt the accuracy of their histories; but because denial of infection was so constant and characteristic of patients in these groups, we were inclined to accept the histories as essentially accurate.

The cause of the nephritis in the five cases in which no obvious focus of infection was demonstrable is not clear. One must accept either the

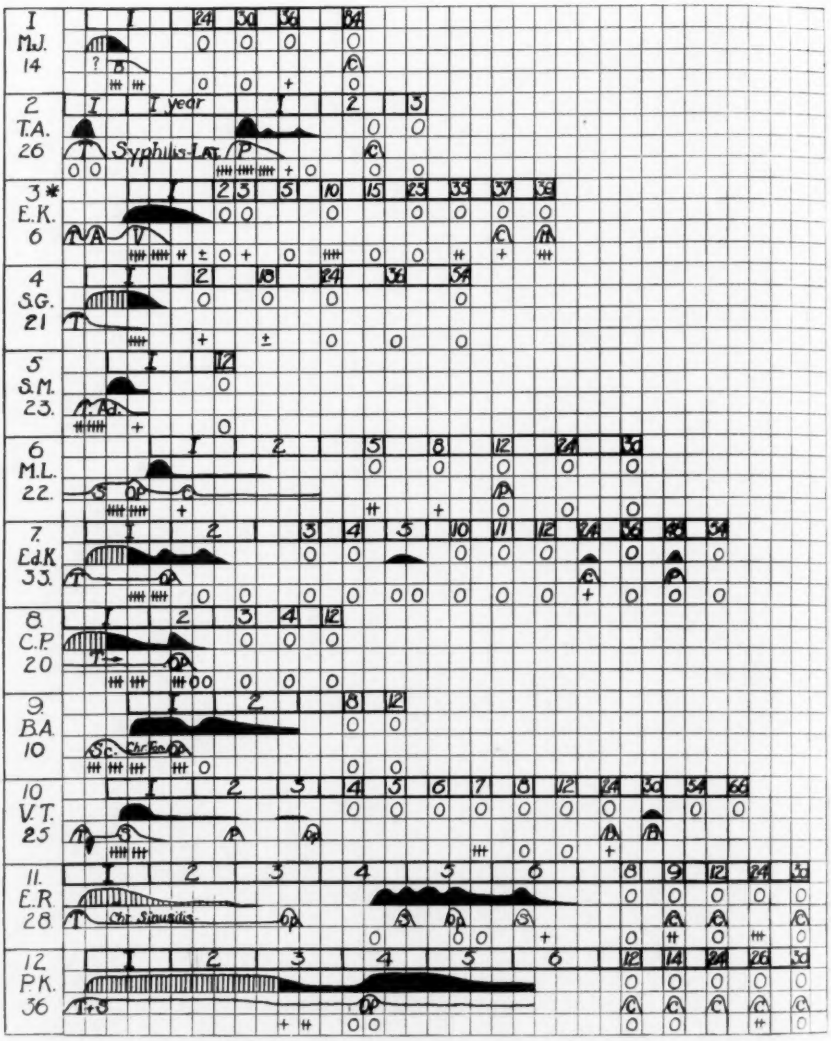

Chart 1.—Part 1.

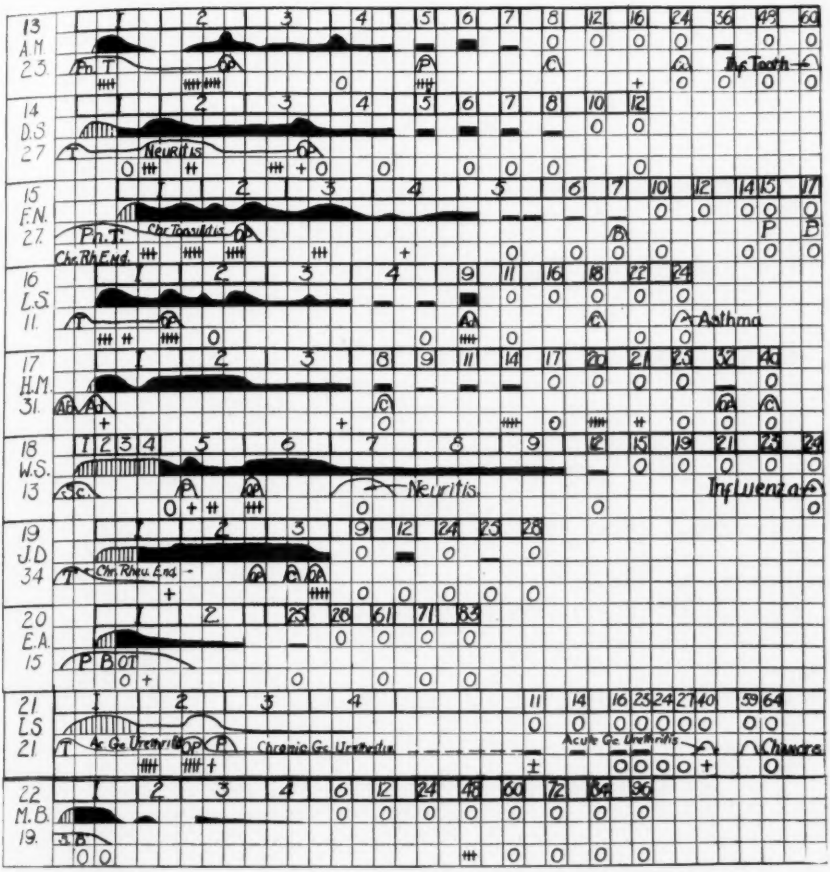

Chart 1.—Part 2.

Chart 1.—Well group. In cases 1 to 21 hemorrhagic nephritis had been associated with the presence of Str. haemolyticus, beta type. In case 22, microorganisms had not been demonstrated to be present.

In charts 1, 2 and 3 four lines have been allotted to each case, representing in order, from top to bottom, the month of the onset of the disease, the general progress of the disease (cross-hatching indicates that prior to our observations; black, that thereafter), the infections observed and the presence or absence of Str. haemolyticus, designated as + or 0, respectively. In the left hand margin are given in order from top to bottom the number of the cases and the initials and age of the patient.

The following abbreviations are employed in the charts: *A*, appendicitis; *Ab*, abscess; *Ad*, adenitis; *B*, bronchitis; *C*, coryza; *D*, dead; *Ery*, erythema; *Gc*, gonorrheal urethritis; *I*, influenza; *M*, measles; *Op*, operation (usually tonsillectomy and adenoidectomy); *P*, pharyngitis; *Pn*, pneumonia; *S*, sinusitis; *Sc*, scarlet fever; *T*, tonsillitis; *V*, varicella.

* Denny, E. R., and Baker, B. M., Jr.: Varicella Complicated by Acute Nephritis, Bull. Johns Hopkins Hosp. **44**:201, 1929.

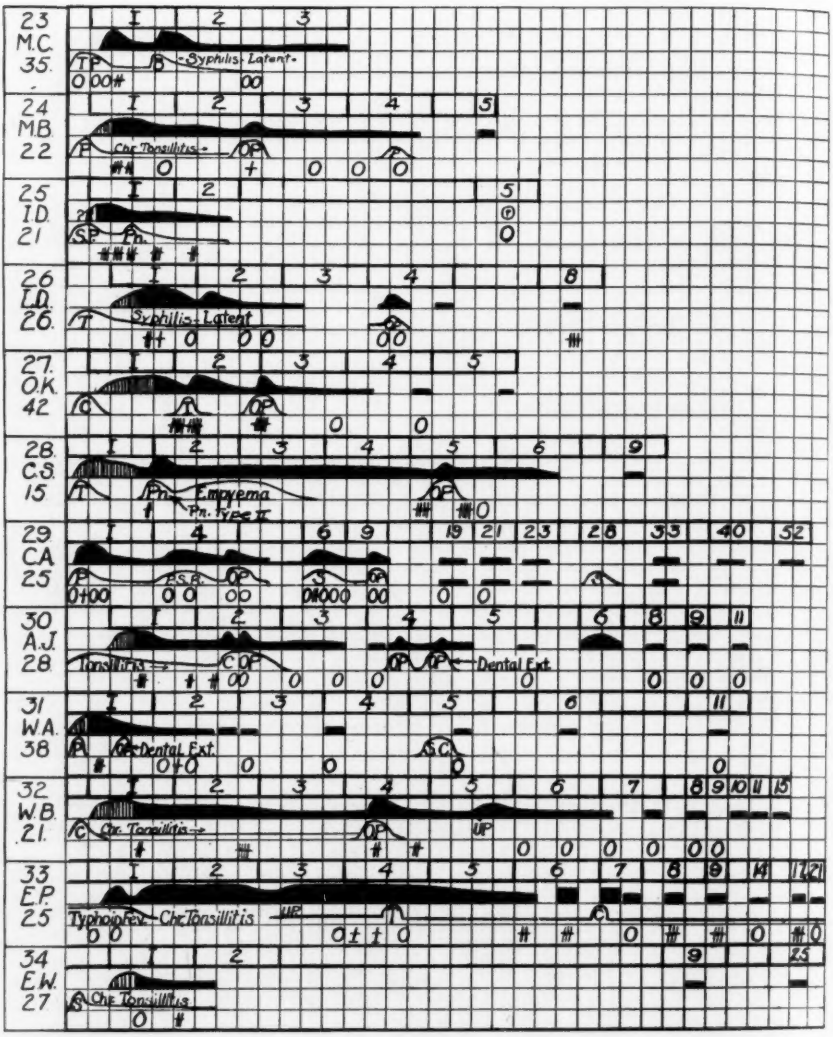

Chart 2.—Part 1.

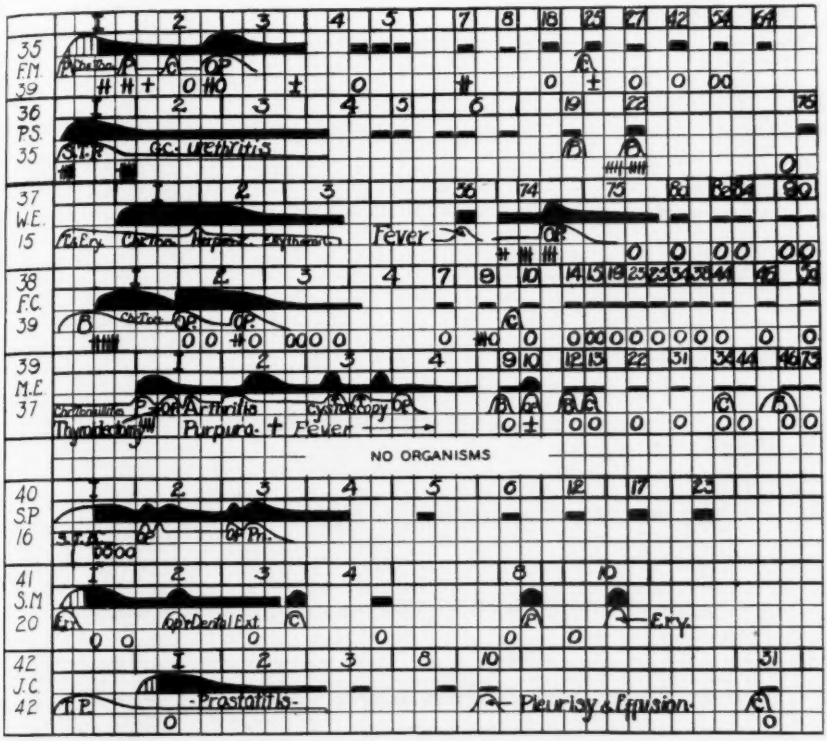

Chart 2.—Part 2.

Chart 2.—Latent group. In cases 23 to 39 hemorrhagic nephritis was associated with the presence of Str. haemolyticus. In cases 40 to 42 infection could not be demonstrated.

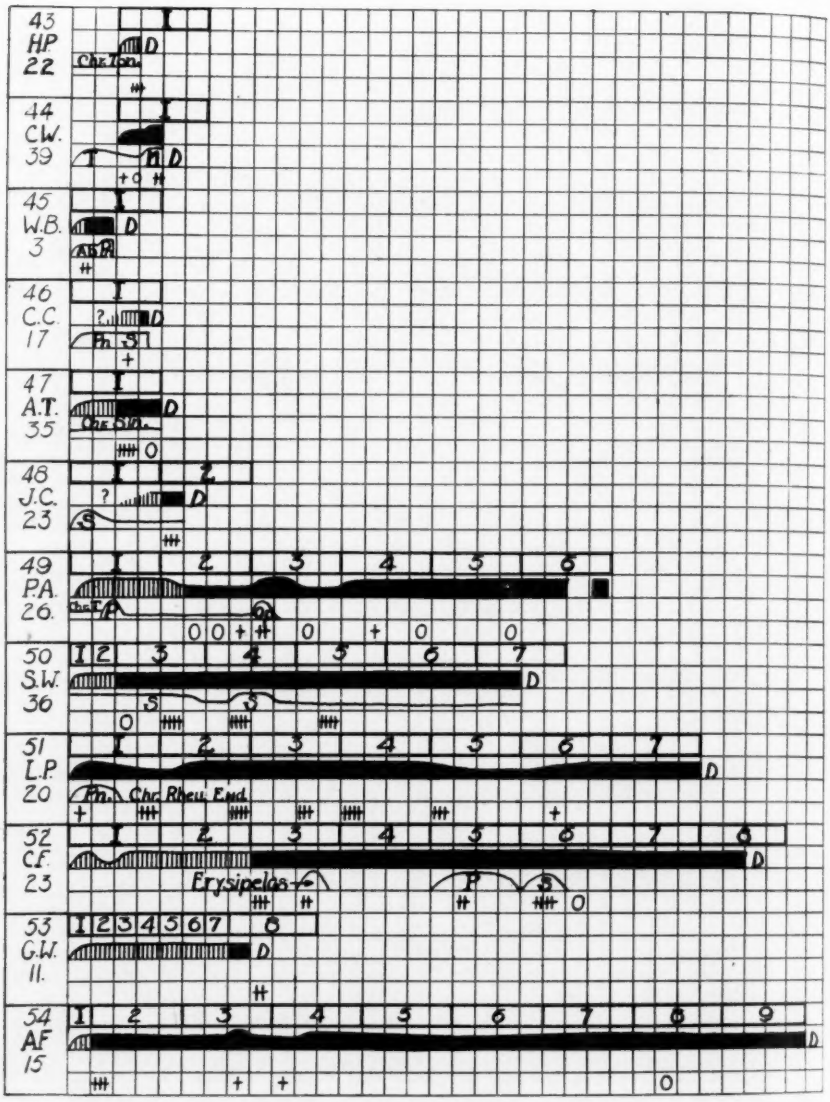

Chart 3.—Part 1.

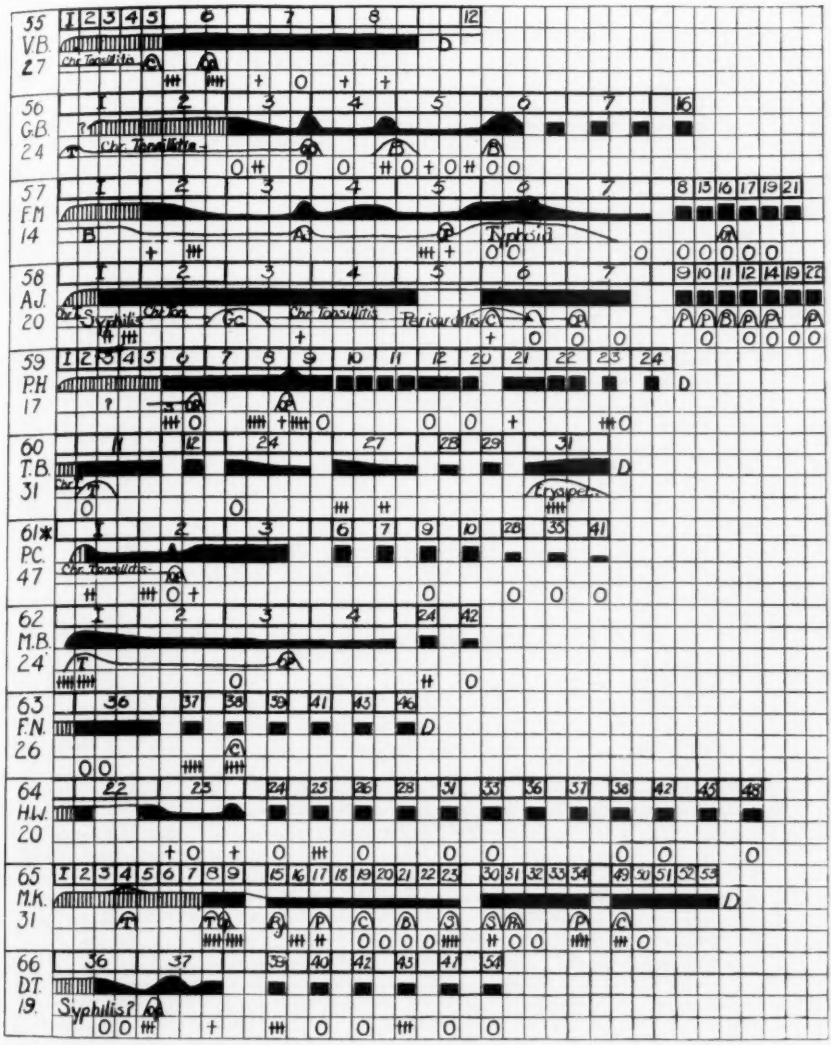

Chart 3.—Part 2.

Chart 3.—Progressive and fatal group. In cases 43 to 66 hemorrhagic nephritis was associated with the presence of Str. haemolyticus, beta type. In cases 67 to 71 hemorrhagic nephritis was associated with the alpha type of the hemolytic streptococcus. In cases 72 to 78 no micro-organisms were demonstrated.

*Now in latent stage of hemorrhagic nephritis.

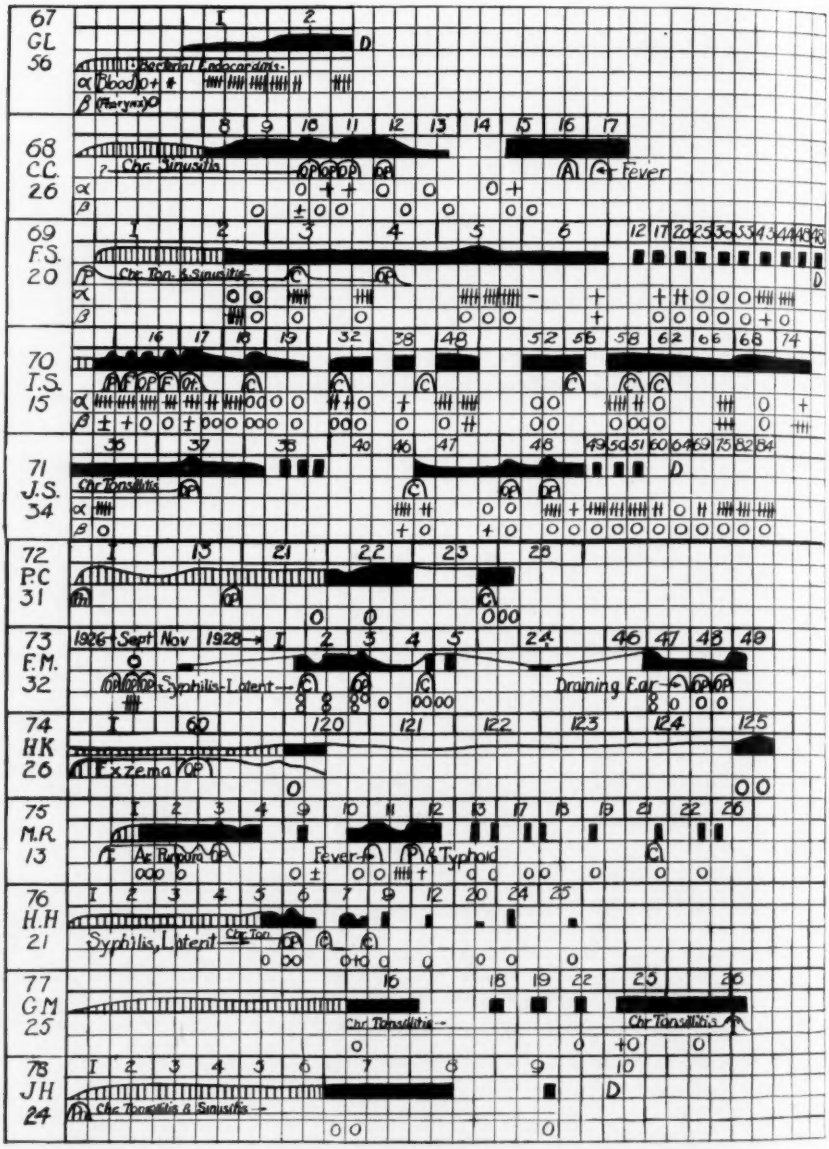

Chart 3.—Part 3.

view that the infections were too mild to attract attention, or the view that nephritis developed without the impetus of infection and was due to causes still unknown.

The possible underlying relationships between acute infection and chronic infection noted at the onset and the ultimate course of nephritis will be discussed later in greater detail.

THE PRODROMAL PERIOD: THE TIME INTERVAL BETWEEN THE ONSET OF INFECTION AND THE ONSET OF HEMORRHAGIC NEPHRITIS

A definite interval of time between the onset of infection and the manifestations of hemorrhagic nephritis in scarlatina has long been recognized. The usual length of this period in scarlet fever, as given by Schick [19] and Goodall,[20] is from three to four weeks. It is also well known that a similar period can usually be demonstrated [21] in cases of hemorrhagic nephritis following infections other than those associated with scarlatina. In this series, only forty-one cases in which acute infec-

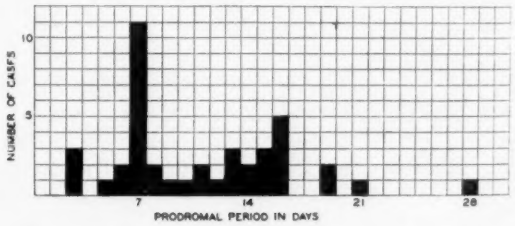

Chart 4.—The prodromal period in hemorrhagic nephritis. This shows the prodromal period in forty-one cases of hemorrhagic nephritis. The ordinates represent the numbers of cases and the abscissas the numbers of days. The prodromal period varied between three and twenty-eight days; the most frequent was seven days, and the average was ten and nine-tenths days. Nephritis developed on or between the seventh and the sixteenth day in thirty-three cases (80 per cent).

tion preceded the onset of nephritis provided adequate data whereby the prodromal period could be determined.

Although the onset of infection and the manifestations of nephritis rarely appeared simultaneously, accurate calculation of the prodromal period was, at best, difficult, and the result represents, in most instances, a mere approximation; for unless the patient is examined carefully each day after the onset of infection, one cannot state definitely the day of onset of the nephritis. Of the forty-one cases, only six devel-

19. Schick, B.: Die Nachkrankheiten des Sharlach, Jahrb. f. Kinderh. **65**:132, 1907.

20. Goodall, E. W.: On the Aetiology and Clinical Aspects of Scarlatinal Nephritis, Guy's Hosp. Rep. **31**:91, 1899.

21. Longcope,[4] Osman [22] and Addis.[23]

oped in the wards, where examinations of the urine were made daily. In the remaining thirty-five cases, the appearance of edema, oliguria or hematuria as noticed by the patient was assumed to mark the day of onset.

Nephritis appeared as early as the third day in three cases, and in one case as late as the twenty-eighth day; in the largest number of cases, eleven, it developed on the seventh day; the average for the whole group was ten and nine tenths days. In thirty-three cases, or 80 per cent of the entire group, the prodromal period fell on or between the seventh and sixteenth days. According to chart 4 there was a progressive decrease in the number of patients in whom nephritis developed during the third and particularly during the fourth week. These figures agree closely with those given by Osman and his co-workers [22] for thirty-six cases of acute hemorrhagic nephritis but differ from the data given by Schick [19] and Goodall [20] for postscarlatinal nephritis and by Addis [23] for hemorrhagic nephritis. In the series presented by Schick and Goodall, the onset of nephritis was noted more frequently during the third week, whereas the weekly frequency among Addis' cases was practically uniform, except for a slight decrease during the fourth week.

Six cases (2, 5, 6, 9, 22, and 44) were followed closely during the prodromal period in the wards, but the number was too small to serve as controls for the larger group of thirty-five cases. The prodromal period in these six cases varied greatly. The shortest was five and the longest nineteen days, with an average of twelve and three tenths days. The latter value was in close agreement with the average for the whole group.

DURATION OF ACTIVE INFECTION AT THE ONSET OF NEPHRITIS CORRELATED WITH DURATION OF THE ACTIVE STAGE OF NEPHRITIS

Table 5 suggests that there was a direct relationship between the duration of acute or active infection and that of the active phase of nephritis only in the group that went on to recovery; no such conditions apparently obtained in the group that became latent, although the average duration of the active phase in the two groups was approximately equal. Because of the presence of chronic infection in the progressive and fatal group, comparison of the duration of active infection with that of active nephritis was impossible, unless one considers progressive nephritis as the active phase in this type of Bright's disease.

---

22. Osman, A. A.; Close, K. G., and Carter, H.: Studies in Bright's Disease: Observations on the Aetiology of Scarlatinal Nephritis, Guy's Hosp. Rep. **83**:360, 1933.

23. Addis, T.: Haemorrhagic Bright's Disease, Bull. Johns Hopkins Hosp. **49**:271, 1931.

SEASONAL VARIATION IN THE ONSET OF HEMORRHAGIC NEPHRITIS

The onset of hemorrhagic nephritis, as represented in table 6, occurred more frequently during the fall, winter and spring months: fifty-four cases in the interval from September to April, inclusive, as compared with fifteen in the period from May to August. This seasonal variation coincided with waves of infections of the upper respiratory tract occurring in Baltimore, and this relationship became more

TABLE 5.—*Duration of Active Infection at Onset Correlated with Duration of Active Phase of Nephritis.**

Duration of Active Infection	Well Group		Latent Group	
	Cases	Duration of Active Phase of Nephritis, Weeks	Cases	Duration of Active Phase of Nephritis, Weeks
1 week or less	8	2.5	6	4.1
1 to 2 weeks	7	3.3	10	2
3 weeks or more	6	6	5	4

* Definite correlation between the duration of active infection and the duration of the active stage of nephritis was demonstrable only in the well group; the average duration of the latter period was approximately equal in both groups. Because of the presence of chronic infection in the progressive group a similar relationship could not be determined.

TABLE 6.—*Seasonal Variation in the Onset of Sixty-Nine Cases of Hemorrhagic Nephritis**

Month	Well Group	Latent Group	Progressive or Fatal Group	Total
January	2	1	..	3
February	2	4	2	8
March	3	5	3	11
April	3	3	2	8
May	1	1	2	4
June	1	..	4	5
July	1	1	2	3
August	1	1	1	3
September	..	3	..	3
October	1	..	3	4
November	5	1	2	8
December	1	1	7	9

* It was impossible to state accurately the month of onset in cases 47, 50, 63, 66, 67, 70, 71 and 74 (all of progressive group). The incidence was much greater during the fall, winter and spring months: fifty-four cases from September through April compared with fifteen cases during May and August. This variation was more noticeable in the well and latent groups.

pronounced if one excluded the progressive and fatal group, in which the relatively uniform monthly incidence was related, we believe, to the factor of chronic infection. In the majority of cases in this group nephritis apparently developed without the impetus of acute infection.

INFECTIONS OCCURRING DURING THE COURSE OF HEMORRHAGIC NEPHRITIS EXCLUSIVE OF THOSE AT THE ONSET OF THE DISEASE

Further analysis of the relationship of infection to the progress of nephritis in this series shows that exacerbations of the disease were

in most instances associated with infections of the upper respiratory tract, in which the incidence of Str. haemolyticus was considerably higher than in infections not associated with exacerbations of nephritis.

Difficulty often arises in determining exactly the occurrence of an exacerbation. This is particularly true in the progressive type of the disease wherein variations, although sometimes pronounced, are observed without any discernible cause. An exacerbation of nephritis when associated with overt infection appears usually within twenty-four hours after the infection begins. Case 23 (chart 2) illustrates the difference in duration between the prodromal period occurring prior to the onset of nephritis and that occurring prior to the beginning of an exacerbation. The former was thirteen days. By the twenty-ninth day of the disease, convalescence was apparently established, and the presence of nephritis was revealed only by traces of albumin and a few red blood cells in the urine. On the thirtieth day, acute bronchitis intervened and an exacerbation of the nephritis, marked particularly by a sharp increase of the hematuria, was noted within twenty-four hours. The hemolytic streptococcus, beta type, was recovered from the sputum in almost pure culture. In seven days, the fever, tachycardia, cough and physical signs of the infection had disappeared, and, coincidently, the urine reverted to its original status. The duration of the prodromal period at the onset of acute nephritis was originally compared by Schick [19] and Pirquet [24] with the similar period in the development of serum disease. There is considerable experimental evidence [25] to suggest that during this period a hypersensitive state may develop, which may account for some of the manifestations of streptococcic infection. On the basis of this analogy, we suggest that exacerbations of nephritis following acute streptococcic infections simulate

24. von Pirquet, C. E.: Allergy, Arch. Int. Med. **7**:259 (Feb.) 1911.

25. (*a*) Lukens, F. D. W., and Longcope, W. T.: Experimental Acute Glomerulitis, J. Exper. Med., **53**:511, 1931. (*b*) Hansen-Pruss, O. C.; Longcope, W. T., and O'Brien, D. P.: Skin Reactions to Filtrates of Haemolytic Streptococci in Acute and Subacute Nephritis, J. Clin. Investigation **7**:543, 1929. (*c*) Derick, C. L., and Fulton, M. N.: Skin Reactions of Patients and Normal Individuals to Protein Extracts of Streptococci, ibid. **10**:121 (April) 1931. (*d*) Ophüls, W.: The Aetiology and Development of Nephritis, J. A. M. A. **69**:1223 (Oct. 13) 1917. (*e*) Bell, E. T.; Clawson, B. J., and Hartzell, T. B.: Experimental Glomerular Nephritis, Am. J. Path. **1**:247, 1925. (*f*) Kuczynski, M. H.: Nephritisstudien, Virchows Arch. f. path. Anat. **227**:186, 1920. (*g*) Duval, C. W., and Hibberd, R. J.: Experimental Glomerular Nephritis Induced in Rabbits with the Endotoxic Principles of Streptococcus Scarlatina, J. Exper. Med. **44**:567, 1926. (*h*) Lukens, F. D. W.: Acute Experimental Glomerulitis Following Repeated Injections of Haemolytic Streptococci into the Renal Artery, Bull. Johns Hopkins Hosp. **49**:312 (Nov.) 1931. (*i*) McLeod, N., and Finney, G. G.: Acute Experimental Glomerulitis Following Injections of Streptococcus Viridans into the Renal Artery, ibid. **51**: 311 (Nov.) 1932.

an accelerated allergic reaction, such as that following the injection of horse serum into a subject already sensitized thereto. Definite alterations in the severity of nephritis also occur with other infections, such as pneumonia and typhoid fever, but whether such changes are exacerbations such as occur after streptococcic infections, as described, is doubtful, for by close study it was possible to show that the prodromal period following pneumonia or typhoid fever was longer and the increase in the urinary sediment was less abrupt. This difference was well illustrated in case 75, in which moderate increases in the formed elements of the urine occurred during the first two weeks of typhoid fever, but within thirty-six hours after the beginning of acute pharyngitis, due to Str. haemolyticus, beta type, a sharp increase in albumin and gross hematuria was noted. The changes in nephritis associated with pneumonia and typhoid fever were probably the manifestations of the usual mild renal irritation attendant on any febrile illness; but the sharp, abrupt change coincident with the streptococcic infection suggested a specific relationship between the streptococcic infection and the original cause of nephritis.

Exacerbations of nephritis, usually of a transient character, follow within twenty-four hours after operative procedures (tonsillectomies, adenoidectomies, dental extractions and antrectomies). These exacerbations are always manifested by increases in the urinary sediment, usually by oliguria, in some patients by slight increases in blood pressure, and less often by the increase or appearance of edema. The cause of this reaction cannot be stated definitely. It is not probable that the changes are due to the effect of the anesthesia. It is more likely that the mechanical manipulation of infected tissue may liberate toxic bacterial products sufficient to intensify the renal injury already present. Occasionally reactions after operation are so pronounced and so prolonged as to support the latter suggestion.

One hundred and twenty-six infections, tabulated in table 7, occurred during the course of the disease in this series. Infections of the upper respiratory tract comprised the majority: ninety-five, or 72 per cent. Forty-two infections were associated with exacerbations, and of these, 55 per cent were characterized by cultures positive for Str. haemolyticus, as compared with 30 per cent of the eighty-four infections not accompanied by exacerbations. These differences were not marked, but they indicated that when an infection is followed by exacerbation of nephritis Str. haemolyticus is likely to be found. Exacerbations of nephritis also occurred despite the failure to demonstrate any inciting factor. Of a total of sixty-three exacerbations in the entire series, forty-two, or 66 per cent, were associated with infections; the remaining twenty-one, or 34 per cent, were apparently unrelated to active infections.

In table 8, the total number of infections noted in each of the three groups of cases is correlated with the frequency of the streptococcus and of the exacerbations observed. It may be noted that 67 per cent of the infections inducing exacerbations of nephritis in the well group, and 50 per cent of those in the latent group, yielded the hemolytic streptococcis in culture, whereas only 32 per cent of the infections in the well

TABLE 7.—*Relationship of the Form of Intercurrent Infection to the Course of Nephritis, and of Str. Haemolyticus to Infections Causing Exacerbations*

Infection Observed During Course of Nephritis	Cases	Incidence of Str. Haemolyticus			Incidence of Exacerbations	Incidence of Str. Haemolyticus in Exacerbations		
		+	0	No Culture		+	0	No Culture
Infectious conditions accompanied by exacerbations of nephritis								
Coryza	41	15	21	5	9	4	4	1
Pharyngitis	21	8	8	5	6	3	2	1
Bronchitis	13	6	3	4	5	2	1	2
Sinusitis	9	7	2	..	3	2	1	..
Pneumonia	5	2	3	..	2	1	1	..
Unexplained fever	4	2	2	..	3	2	..	1
Tonsillitis	5	2	2	1	2	1	..	1
Otitis media	3	1	2	..	3	1	2	..
Adenitis	2	2	..	..	2	2	..	..
Erysipelas	2	2	..	..	1	1	..	..
Typhoid fever	2	2	..	..	2	2	..	..
Neuritis	2	1	1	..	1	1	..	..
Measles	2	2	..	..	1	1	..	..
Purpuric arthritis	1	1	..	..	1	1	..	..
Erythema	1	..	..	1	1	..	..	1
Infectious conditions not accompanied by exacerbations								
Urethritis (gonococcic)	4	1	2	1	..	..	..	..
Asthma	1	..	1	..	..	..	..	..
Influenza	1	..	1	..	..	..	..	..
Varicella	1	1	..	..	..	..	..	..
Abscess	2	..	..	2	..	..	..	..
Chancre	1	..	..	1	..	..	..	..
Pleurisy with effusion	1	..	..	1	..	..	..	..
Pericarditis	2	1	..	1	..	..	..	..
Total (23)	126	56	48	22	42	24	11	7

* This table illustrates which infections were associated with exacerbations of nephritis. Respiratory infections comprised the majority—ninety-five, or 72 per cent. Cultures were taken in most instances from the pharynx. Of the forty-two infections associated with exacerbations, 55 per cent were due to the streptococcus, as compared with 30 per cent of the eighty-four infections not inducing exacerbations.

group and 19 per cent of those in the latent group not accompanied by exacerbations showed this organism. This difference in the incidence of the streptococcus in these two groups of infections, with respect to the presence or absence of exacerbations, is sufficiently great to be of significance. In the progressive and fatal group, on the contrary, the streptococcus persisted, irrespective of whether or not acute infections were followed by exacerbations, which indicates that the patients were chronic carriers of the organism.

Of the exacerbations not accompanied by active infection, six occurred during convalescence, four during the latent and eleven in the progressive stage of the disease. It is of interest that the incidence of the streptococcus was considerably lower in these exacerbations than in those accompanied by active infections.

It also may be noted in table 8 that the relative number of infections in each group of cases was approximately equal, but that exacerbations of nephritis associated with infection were more frequent in the latent and progressive groups. In the well group, 25 of the 37 infections were contracted after complete recovery from nephritis was established, and it is important to observe that in only one case (7) on two occa-

TABLE 8.—*Correlation of the Total Number of Infections Noted in Each of the Three Groups of Cases with the Frequency of Str. Haemolyticus and of Exacerbations*

	Well Group (22 Cases)	Latent Group (20 Cases)	Progressive or Fatal Group (36 Cases)
Infections			
Total number	37	30	58
Number associated with exacerbations	9 (24%)	14 (45.6%)	19 (33%)
Number not associated with exacerbations	28 (76%)	16 (53.7%)	39 (67%)
Results of cultures from Str. haemolyticus			
Infections associated with exacerbations			
Positive	6 (67%)	7 (50%)	11 (52%)
Negative	2 (22%)	3 (21%)	6 (37%)
No culture	1 (11%)	4 (29%)	2 (10%)
Infections not associated with exacerbations			
Positive	9 (32%)	3 (19%)	19 (37.5%)
Negative	15 (54%)	8 (50%)	15 (37.5%)
No culture	4 (14%)	5 (31%)	5 (25%)

sions were significant abnormalities found in the urine; twenty-three infections (five of which were due to Str. haemolyticus) had no apparent adverse effect so far as nephritis was concerned. It is obvious, then, that infections arising during the convalescent stage do not necessarily prevent recovery, and after recovery has been established, do not cause relapses of nephritis; on the other hand, exacerbations are more frequently associated with streptococcic infections in the latent and progressive stages. This suggests that patients who are destined to recover from nephritis become refractory or immune to infections during the convalescent stage and remain so after recovery has occurred; whereas in the latent and progressive stages this is not true, for the patient then appears to be more sensitive to streptococcic infections.

Further analysis of the progressive group shows that many patients with the chronic form of hemorrhagic nephritis presented recurring or chronic streptococcic infection (cases 56, 60, 63, 50, 51, 52, 68, 70 and 75), while an equal number showed only the streptococcus, and infections were insignificant (cases 49, 53, 56, 50 62, 64, 66, 69 and 71) ;

in a smaller number, infection occurred, but the streptococcus was not found (cases 57, 58, 73, 76 and 78); only four patients failed at any time to show either infection or the streptococcus (cases 54, 61, 72 and 74). With the exception of the few patients in whom the streptococcus was never obtained, the presence and persistence of this organism were characteristic of this stage of the disease, even though manifestations of infection were absent. Whether the mere presence of the streptococcus in the pharynx of patients in whom infections were not demonstrable is of significance in causing a continuation of the nephritis and can be interpreted as an actual chronic infection cannot be answered at present. It should be emphasized, however, that recurring active streptococcic infections or the "carrier state" (a total of 66 per cent of patients with progressive nephritis in contrast to 15 per cent of persons in the general population) and the absence of acute active infection at the onset are the chief characteristics of this chronic type of nephritis. Furthermore, the absence of demonstrable infection does not necessarily mean that infection is not present. Occult infection may exist, particularly in the accessory nasal sinuses, and may be important in this type of the disease, as in case 69, which showed chronic infection of the ethmoid cells, discovered only at postmortem examination.

EFFECT OF OPERATIVE PROCEDURES ON THE INCIDENCE OF: RECURRING INFECTIONS, STR. HAEMOLYTICUS, EXACERBATIONS OF NEPHRITIS, THE NATURAL HISTORY OF NEPHRITIS

If infection initiates hemorrhagic nephritis, the logical procedure which might conceivably exert a beneficent influence on the progress of the disease seems to be the removal of the infected tissue or tissues. Such an opinion was held by Longcope [4] and Platt,[26] and vigorous effort to this end has been made. The object theoretically to be attained by such procedures is the elimination of the infected tissues and the infecting organism.

Operative procedures were performed with the close cooperation of Dr. Crowe and his staff in forty-nine cases in this series: forty-three were tonsillectomies and adenoidectomies, of which four were combined with antrectomy; two were dental extractions, and four were operations on the accessory nasal sinuses only. Unfortunately, there were only sixteen cases in which infections were presented for which operative procedures might have been performed but for several reasons were not. Although realizing that this number is too small to serve as an adequate control group, we have, nevertheless, presented the group as a basis for comparison with the operative cases. The data covering the time of operation (month of disease), the number of patients exhibiting postoperative infections and exacerbations of nephritis and the pre-

operative and postoperative incidence of the hemolytic streptococcus in both groups are sumarized in table 9.

This table shows that elimination of foci of infection apparently did not prevent either postoperative infections or exacerbations of nephritis, since the average number of each was greater in the operative than in the nonoperative cases. Furthermore, operation did not appear to influence the incidence of the streptococcus in the nasopharynx; there was an apparent postoperative decrease in the well and latent groups, but there was also a parallel reduction in the patients of these two groups who were not operated on; in fact, six of the seven well

TABLE 9.—*Effect of Operative Procedures on the Incidence of Postoperative Infections, Exacerbations and Str. Haemolyticus*

	Group Operated On								
							Str. Haemolyticus		
Stage of Nephritis	Cases	Time of Operation, Month of Nephritis	Cases with Postoperative Infection	Infections per Case, Average	Cases with Exacerbations	Exacerbations per Case, Average	Preoperative	Tissue from Operation	Postoperative
Well	14	2.4	10	2.6	5	1.8	13	10	6
Latent	16	2.6	8	2	3	1.6	13	9	5
Progressive or fatal	19	12.3	11	3.2	7	1.5	13	8	14

	Group Not Operated On						
						Str. Haemolyticus	
Stage of Nephritis	Cases	Cases with Infection after Active Stage of Nephritis	Infections per Case, Average	Cases with Exacerbations after Active Stage	Exacerbations per Case, Average	Active Stage	Well, Latent and Progressive Stages
Well	7	3	1	0	0	6	1
Latent	5	4	1.5	1	—	4	2
Progressive or fatal	4	4	1.2	1	—	2	3

patients who were not operated on eventually showed negative cultures. Because of the inadequate number of controls (patients who were not operated on) one might accept the decreased incidence of the streptococcus in the well and latent groups as related to the operative procedures; if so, then a parallel diminution should be expected in the progressive and fatal group, but table 9 reveals that the incidence remained unchanged, irrespective of whether or not operation was done. The decrease of this organism in the former two groups and its persistence in the latter group, we believe, are related more nearly to the resistance of the patients to the infecting organism than to the operative procedures.

Since a larger number of the cases in the progressive and fatal group came under observation at later stages than the cases in the other two groups, it is possible that a delay in instituting surgical measures might explain the persistence of the streptococcus, and perhaps, indirectly, the progressive nature of the disease in these cases. Operation in this

group was performed usually during the twelfth month of the disease, or approximately ten months later than in the well and latent groups. The four progressive cases in the control group were too small a number to refute this point. Of the nineteen progressive cases in the other group, however, operation was performed in six during the second and third month, and in four during or before the sixth month of the disease. The possibility, therefore, that delay in operation was responsible for the persistence of the hemolytic streptococcus and the progression of nephritis seems unlikely. The patients in the series of cases reported recently by Platt [26] (1932) were apparently benefited by operation, but he presented no control cases, and no differentiation was made between the effect of operation in cases in which there was eventual recovery, in those which remained latent or in those which became progressive. Moreover, the course of the disease in individual cases, as described by him, differed in no manner from the progress of the disease in cases of our nonoperative group. Although it is possible that acute recurrences of a streptococcic infection and of nephritis may be prevented by operative procedures, such as tonsillectomy, it appears that factors other than the operative attempt to eliminate foci of infection must account for recovery or progression in nephritis.

COMMENT

The view that streptococcic infections cause hemorrhagic nephritis is given strong support by the evidence presented in the analysis of this series of cases. These infections, as in other series, are confined almost entirely to the respiratory tract. It is true, however, that a small number of patients, four, all with the progressive type of the disease, failed to show active infection at any time during its course, although four of the five carried the streptococcus in their respiratory passages. However, it will be of interest eventually to determine, if possible, the significance and importance of the mere presence of the streptococcus in relation to both the cause and the progress of nephritis; for it is not improbable that the "carrier state" is a condition sufficient in itself to incite the disease without producing objective evidence of infection.

The bacteriologic data are confined, however, to the incidence of Str. haemolyticus. That other organisms, such as the typhoid bacillus or the pneumococcus, cause nephritis is not denied, but we found no evidence in this series, with the possible exception of case 33, to support this view. With the exception of the cases of pulmonary infections,

26. Platt, Robert: The Effect of Removal of Septic Foci on the Course of Nephritis, Quart. J. Med. **1**:499, 1932.

detailed identification of bacteria other than the streptococcus was not carried out, and it is possible that other organisms may eventually be found to explain both the cause of nephritis and the inability to demonstrate the streptococcus in the eleven cases in which this organism was not found.

In addition to the bacteriologic aspects of the infections associated with acute hemorrhagic nephritis, further interesting relationships between infection and this disease were developed in this study. Hitherto, attempts to explain the influences, favorable or unfavorable, on the course of nephritis have concerned themselves with four factors: (1) the recurrence or persistence of the causative infection, (2) the persistence of the streptococcus, (3) the elimination of foci of infection and (4) the age of the patient. On the basis of this analysis, we suggest a fifth factor, namely, the character of the infection at the onset of nephritis. The analysis in the section dealing with the character of the infection at the onset of nephritis (p. 304) revealed that patients in whom nephritis developed after an acute infection accompanied by definite constitutional symptoms usually recovered, or their nephritis entered the latent stage; whereas in patients with nephritis associated at the onset with chronic infection the disease usually became progressive.

The first and second factors were discussed and emphasized by both Addis [23] and Longcope.[4] It was shown, however, that recurring infections, in spite of their relation to exacerbations, do not necessarily determine the ultimate outcome of the disease, for partial recovery to the latent stage or complete recovery from nephritis was not prevented by such infections, and whereas the progressive group was characterized by recurring infections in some cases, in others this factor was not obvious, and in a few patients active infection was never demonstrated. The presence of Str. haemolyticus in the respiratory tract does, however, vary with the stage of the disease, for it diminishes with recovery but persists during the progressive phase. It has been suggested that perhaps the mere presence of this organism may be sufficient to explain the progressive nature of nephritis, even though active infection is absent. We feel, however, that the variation in the incidence of the streptococcus during the course of the disease may be only one manifestation or result of some basic factor associated with the reaction of the patient to infection. The attempt to eliminate foci of infection by operative procedures is not always successful in the prevention of subsequent infection or exacerbations of nephritis, in influencing the frequency with which the streptococcus is found in the respiratory tract or in determining, eventually, recovery from or progression of the disease. It has long been recognized that hemorrhagic

nephritis in children, as recently reviewed by Guild,[27] very rarely progresses to the chronic stage. No difference, however, in the average age of our three groups of patients, as given in table 10, was found. It is interesting to note with respect to this question that in Guild's series of thirty-four carefully studied cases definite acute infection preceded the onset of nephritis in thirty cases, and chronic infection in only four cases. By analogy, one is inclined to suggest that the outcome of nephritis in children is related to the character of the causative infection, as well as to the age of the patient.

It has seemed to us that the presence or absence of active infection at the onset of nephritis is of greater significance in explaining eventual progress of the disease than the other four factors combined. If this assumption is true, it is suggested that patients in whom both local and constitutional manifestations of acute infection develop possess the

TABLE 10.—*Decades of Life of Seventy-Seven Patients with Hemorrhagic Nephritis* *

Age, Years	Well	Nephritis Latent	Nephritis Progressive or Fatal
1-10	1	..	1
10-20	6	4	9
20-30	11	8	16
30-40	4	7	8
40-50	..	1	1
Average age	22	28	25

* The frequency of nephritis increased with age through the third decade, then decreased. There was a relatively equal distribution of well patients, patients with latent nephritis and patients with progressive or fatal nephritis in each decade. Age, therefore, in this series, was not a primary factor in the prognosis of nephritis.

capacity to react to the infecting organism, and owing to or as a result of this reaction, a resistance to the infection is acquired; thereafter, recurring infections are usually without influence, so far as the nephritis is concerned, recovery from the disease ensues, and simultaneously the streptococcus disappears. Excellent examples among the nineteen of twenty-one well cases, and nineteen of twenty latent cases, which illustrate this point are cases 2, 15, 21 and 23. In progressive nephritis, on the other hand, the capacity to react to the infecting organism is lacking. Both local and constitutional manifestations of active infection are therefore slight, a state of immunity to the streptococcus does not develop, and consequently either recurring streptococcic infection or merely the "carrier state" persists as a manifestation of the chronic stage of the disease. Typical among the twenty cases of progressive nephritis illustrative of this are cases 49, 57, 65 and 71.

27. Guild, H. G.: The Prognosis of Acute Glomerular Nephritis in Children, Bull. Johns Hopkins Hosp. **48**:193, 1931.

Recovery from nephritis depends, therefore, according to the foregoing suggestion, largely on the capacity of the patient to react favorably to infection. This may account for the favorable outcome in children. Although operative procedures may hasten the cure of infection and the elimination of the infecting organism in some cases, the ultimate favorable result depends on the capacity of the patient to establish some form of resistance to infection by the hemolytic streptococcus. Disappearance of the streptococcus in cases that go on to recovery and in cases which become latent, and persistence of the organism in the progressive stage of the disease, might, therefore, be manifestations of the presence or absence of resistance to infection.

SUMMARY AND CONCLUSIONS

An analysis of the relationship between infection with Str. haemolyticus and hemorrhagic nephritis in a series of seventy-eight cases observed for from one to eight years is reported. Twenty-two of the patients are well, twenty-one are in the latent stage of the disease, seventeen are in the progressive stage and nineteen are dead.

Infections, usually of the upper respiratory tract, caused by Str. haemolyticus (alpha type, in a few cases), preceded the onset of hemorrhagic nephritis in the great majority of cases in this series.

Pneumococcic pneumonia, rheumatic fever and syphilis were not considered as a cause of hemorrhagic nephritis in this series.

Str. haemolyticus is apparently related to the progress of nephritis; for the numbers in which it occurred diminished markedly during recovery but persisted during the progressive stages of the disease. In eleven cases, however, hemolytic streptococci were not shown at any time during the course of the disease.

The cases of hemorrhagic nephritis which were preceded by acute infection manifested by both local and constitutional reactions almost always ended in recovery or entered the latent phase; the cases of nephritis associated with chronic infection at the onset almost always became progressive.

The prodromal period between the beginning of infection and the onset of nephritis varied from three to twenty-eight days; the most frequent interval was seven and the average was ten and nine-tenths days.

A seasonal variation in the onset of hemorrhagic nephritis coincided with months during which respiratory infections are most frequent in Baltimore.

Exacerbations of nephritis in most instances followed streptococcic infections of the upper respiratory tract; these exacerbations occurred more frequently in the latent and in the progressive stages of the disease. The prodromal period between infection and the exacerbation

of the nephritis was usually from twenty-four to forty-eight hours, in contrast to the prodromal period at the onset of nephritis. Exacerbations also occurred without relation to infection, and also after operative procedures.

Streptococcic infections which occurred during the convalescent stage did not prevent recovery from nephritis; and after recovery was established they rarely caused relapses; whereas the "carrier state," with or without recurring evidences of active infection, was characteristic of the progressive stage of hemorrhagic nephritis.

Surgical removal of foci of infection may fail to influence the outcome of hemorrhagic nephritis.

It is suggested that recovery from or progression in hemorrhagic nephritis is related more to the character of the causal infection; a severe acute infection presages a favorable course; a chronic infection, an unfavorable outcome. It is also suggested that patients with acute infection possess the capacity to react to Str. haemolyticus, so that some form of resistance to the infection develops, and as a result recovery from nephritis follows and disappearance of the organism occurs. In patients with chronic infection, this capacity to react to streptococcic infection is lacking, a resistant state does not develop, and as a result the organism persists and the nephritis becomes chronic.

Dr. Warfield T. Longcope permitted us to analyze his carefully studied series of cases of hemorrhagic nephritis and also gave many suggestions and helpful criticisms in the preparation of the manuscript.

THE VISCEROGALVANIC REACTION

E. A. SPIEGEL, M.D.
AND
M. G. WOHL, M.D.
PHILADELPHIA

The differential diagnosis of visceral diseases is often aided by a study of the associated referred pain of the hyperalgetic zones of the skin and the tender areas of the muscles. Such a study, however, fails in many cases because the subjective complaints of the patients may be unreliable. It is desirable in such cases to localize pain by objective methods. It is known from the work of Head [1] and of MacKenzie [2] that diseases of visceral organs produce many reflexes in the skin, such as viscerovasomotor and visceropilomotor reflexes. There are also segmental reflexes from the viscera which cause localized hypertonicity of certain muscles, the so-called visceromotor reflexes. These phenomena are of clinical importance; however, they are not always found. A more delicate objective method for the demonstration of referred pain in cases of visceral disease seems therefore to be desirable.

In such cases the segments of the spinal cord corresponding to the organ involved are in a state of hyperexcitation. This hyperexcitation involves both the somatic and the vegetative segmental centers, as shown by the hyperalgetic zones and the aforementioned reflexes. Consequently, increased nerve impulses are carried not only along the motor nerves but also along centrifugal vegetative nerves to different vegetative organs, e. g., in the skin. Excitation of the vegetative centers induces an increase of the electric potentials of the skin, as shown in psychic excitation, viz., by emotion (Tarchanoff's [3] phenomenon), or in artificial stimulation of the various parts of the central nervous system (Langworthy and Richter [4] and others). It seemed, therefore, probable that the increased excitation of the segmental centers associated with referred

The expenses of this study were partly defrayed by a grant from the Ella Sachs-Plotz Foundation.

From the Department of Experimental Neurology, D. J. McCarthy Foundation and Department of Medicine, Temple University Medical School.

1. Head, H.: Brain **16**:1, 1893; **17**:339, 1894; **19**:153, 1896. Head, H., et al.: Studies in Neurology, New York, Oxford University Press, 1920.

2. MacKenzie, J.: Symptoms and Their Interpretation, London, Shaw & Sons, 1920.

3. Tarchanoff: Arch. f. d. ges. Physiol. **46**:46, 1890.

4. Langworthy, O. R., and Richter, C. P.: Brain **53**:178, 1930.

pain becomes manifest by an increase of the electric potentials in the corresponding dermatomes. Such a reaction was indeed found and was called viscerogalvanic reaction in a preliminary report made by us.[5] A more detailed account of this phenomenon is given in the present paper.

METHOD

The electric potential of the skin is measured by the so-called compensation method, i. e., by opposing to this potential a known variable potential. As long as one electromotive potential is stronger than the other a current will flow which may be indicated by a sensitive galvanometer. When the known variable potential is as strong as the potential of the skin, the galvanometer will show no deflection. A Leeds and Northrup portable galvanometer or a Sanborn string galvanometer was used. A control box with a neutralizer similar to those used in making electrocardiograms provided the variable potential. This neutralizer was standardized so that the number of millivolts furnished by it at each position of its knob was known.

The area of the skin to be studied was first connected with the galvanometer, and thus a deflection occurred. The neutralizer was then rotated until the galvanometer was brought to the zero point. This position of the neutralizer indicated the strength of the electric potential of the skin. Two nonpolarizable electrodes were used. They consisted of silver plates 2.5 by 4 cm. which were coated with silver chloride. Between the electrodes and the skin, gauze soaked in normal potassium chloride was employed, as recommended by Keller.[6] In a few cases a 10 per cent solution of sodium chloride was used. One electrode was fastened by bandage under constant pressure to the ventral side of one forearm of the patient or to the forehead[6a] and the other (testing) electrode was applied to various sites to be studied. It is extremely important to apply the latter electrode on the skin with as little pressure as possible. The metal electrode was therefore provided with an insulated handle; one half of the gauze was fixed on the metal plate by rubber rings and the other half hung freely down. The latter half of the gauze was laid on the skin, while the metal electrode was held in such a way that only its edge touched the skin.

It is important to have the patient completely relaxed so as to avoid errors due to muscular contractions; furthermore, the patient should be in a warm room to avoid reflexes of the skin from cold air, and the bed on which the patient lies should be insulated with glass cups. The electrodes are to be applied to each area for approximately the same length of time, since the potentials are usually lowered by longer or by repeated application of the electrodes. Very hairy patients have to be shaved several days before the examination.

The sensation of the skin was tested, as a rule, after the record of the potentials was taken. Thus, these records were not influenced by mechanical irritation of the skin due to the examination for sensation nor by previous knowledge of eventual hyperalgetic zones.

---

5. Spiegel, E. A., and Wohl, M. G.: Klin. Wchnschr. **11**:1272, 1932.

6. Keller, P.: Arch. f. Dermat. u. Syph. **162**:582, 1930.

6a. The uniform pressure maintains the potential on this site at a low figure. This is far more desirable for the patient than to destroy the epidermis as recommended by Keller in order to bring the potential of the skin to zero.

Thirty-two patients with abdominal or thoracic pain were examined, and fifteen without visceral disease were used as controls. Among the first group there were eight patients with angina pectoris, ten with gastric or duodenal ulcer, one with spastic colitis, one with chronic appendicitis, four with subacute cholecystitis, seven with nephrolithiasis and one with pulmonary tuberculosis.

TABLE 1.—*Measurements of the Potentials of the Skin on Fifteen Controls*

			Skin Potentials, Millivolts						
			Left			Right			
Name	Sex*	Disease	Face	Trunk Min.-Max.	Lower Extremity (Thigh)	Face	Trunk Min.-Max.	Lower Extremity (Thigh)	Comment
B. L.	♀	Adiposity.....	9	1-18	7	14	1-13	1	
C. V.	♀	Diabetes mellitus	21	6-13	6	21	7-23	3	
D. A.	♀	Neurosis.....	32	17	27	35	16	23	
E. B.	♀	Hyperthyroidism	8	3-14	17	19	6-10	10-13	
E. P.	♀	Hysteria.....	9	2-19	12	13	3-19	13	Determination made 1/26/32
			9	7-18	6	13	12-15	17	Determination made 2/9/32
G. L.	♀	Hypothyroidism	4	3-14	6	7	1-14	5	
G. R.	♀	Adiposity.....	17	12-31	20	22	12-31	22	Desiccated thyroid 3 grains daily for 1 week; maximum around umbilicus
H. R.	♀	Epilepsy.....	12	8-10 mamma, 24	0	14	5-7 mamma, 29	0	
L. A.	♂	Enuresis nocturna; mastodynia (left side)	10	7-14	4	5	6-14	5	Mamma, left side, 18; mamma, right side, 6
M. K.	♂	Myxedema.....	31	10-13	8	29	4-9	7	Determination made 3/1/32
			14	5-11	14	15	7-13	9	Determination made 3/5/32
M. S.	♀	Hypothyroidism (postoperative)	35	5-23	12	33	14-22	11	Under thyroid medication; determination made 2/9/32
			18	10-13	5	14	12-13	11	Determination made 3/5/32
P. H.	♀	Dysmenorrhea...	25	11-21 (subclavicular)	13	31	12-14	13	Rouge on face
S. G.	♂	Hypothyroidism	20	23	26	18	14	31	Without thyroid medication for 3 weeks
S. V.	♂	Neurosis.....	19	5-16	17	15	5-21	15	Maximum around nipple
M. G.	♂	Normal.....	0	3-13	..	0	3-4		

* ♀ indicates female and ♂, male.

RESULTS AND COMMENT

The measurements of the potentials of the skin of our fifteen control patients without painful visceral disease are summarized in table 1.

The measurements show considerable differences in different areas of the body, even in a normal person, as already pointed out by Munk

TABLE 2.—*Potentiometric Measurements of the Skin in Visceral Diseases with Referred Pain* *

Case	Name	Sex	Date	Diagnosis	Hyperalgetic Zone	Skin Potentials, Millivolts		Comment
						Left	Right	
1	B.	♂	1/29/32	Spastic colitis	d8-d12 (maximum, upper portion of left side of abdomen)	d4-6 : 4-17 d8 : 25 d9 : 34(+17) d12 : 23 L2 : 15	d4-6 : 10 d9 : 30(+20) d12 : 29 L2 : 13	
2	B. F.	♂	4/23/32	Duodenal ulcer	No	c4-d6 : 10-28 d8-9 : 27 d10-12 : 32(+4) L2 : 16	c4-d6 : 20-22 d8-9 : 29 d10-12 : 31(+9) Right leg amputated	
3	C. A.	♀	2/23/32	Duodenal ulcer	No cutaneous hyperalgesia; only pain on pressure in epigastrium	V-d4 : 23-25 d8-9 : 11 d10-12 : 15 L2 : 20	V-d4 : 17-19 d8-9 : 34(+15) d10-12 : 30 L2 : 13	
4	C. J.	♂	5/ 9/32	Cholecystitis	d8 (right > left)	V : 9 c7 : 19 d2-d9 : 3-8 d11-12 : 22	V : 5 c7 : 23 d4 : 19(mamma) d2-7 : 4-8 d9 : 11 d11-12 : 20	
5	D. W.	♂	2/ 6/34	Nephrolithiasis	Anterior surface: d12-L2 (left) d12-L1 (right) (left > right)	V-d8 : 0-23 d10 : 40(+17) d12-L2 : 38	V-d10 : 10-28 d12 : 47(+19) L2 : 33	
					Posterior surface: d10-12 (slight; left > right)	c4-d9 : 0-7 d10-12 : 30(+13) d12-L1 : 15 s2 : 16.5	c4-d9 : 0.7 d10-12 : 11 d12-L1 : 5 s2 : 15	
6	F. R.	♂	11/ 7/33	Cholelithiasis; apical tuberculosis	d9-10 (slight) c4 (both sides)	Face : 4-8 c4 : 23 d4-6 : 16 d9-10 : 18 d11-L2 : 4-8	V-L2 : 0-7 Only c4: 19(+12)	
7	F. B.	♂	4/ 5/32	Gastric ulcer	Very slight hyperesthesia in the epigastrium (d6-7)	d2-7 : 23 d8-9 : 35(+12) d11-12 : 26 L2 : 14	d2-7 : 29 d8-9 : 23 d11-12 : 27 L2 : 18	

8	G. S.	♂	11/18/32	Functional hyperacidity; chronic appendicitis	Very slight, d10	Maximum d9-10			Accurate figures of potentials unobtainable
9	M. W.	♀	4/22/32	Gastric ulcer	No	V : 27 d2-6 : 12-14 d9 : 7 d12 : 21		V : 21 d2-6 : 21 d9 : 14 d12 : 12	
10	G. A.	♀	2/ 1/33	Cholecystitis	Anterior surface: d8-9	V-d7 : 1-4 d9-10 : 9(+5) d10-12 : 8 L2 : 3		V-L2 : 1-5 d10-12 : 7(+2)	10% sodium chloride
					Posterior surface: d8-10	c4-d6 : 9-11 d8 : 13 d11 : 12.5 d12 : 9		c4-d8 : 3-9 d11 : 13.5 d12 : 12.5	
11 (fig. 1)	L. M.	♂	3/30/32	Duodenal ulcer	Slight hyperesthesia; d7-8 and d11 (right side)	V : 13 d2-10 : 0 d12 : 7 L2 : 25		V : 5 d2-4 : 0 d8 : 9 d11-12 : 36(+27) L2 : 26	
			4/13/32	.....	d8 on the left side more marked than on the right	V : 14 d2-3 : 29 d8-9 : 35(+5) d11-12 : 32 L2 : 10		V : 26 d2-5 : 23-28 d8-9 : 21 d10-12 : 26 L2 : 3	
12	M. J.	♂	1/25/33	Gastric ulcer	d6-7	V-d4 : 1 d7-12 : 3(+2) L1 : 1		V-d4 : 1-2 d7 : 3(+1) d9-12 : 1 L1 : 2	10% sodium chloride
13	M. B.	♀	11/26/32	Pulmonary tuberculosis; duodenal ulcer	c4-d2 (left side) d6-8 (epigastrium, slight)	V : 7 d2 : 108(+49) d5 : 32 d8 : 39 d10-12 : 59		V : 32 d2 : 92(+8) d5 : 20 d8 : 2 d10-12 : 84	
14	M. B.	♀	4/18/34	Nephrolithiasis	d12-L1 (left, only on back)	Anterior surface: c4-d10 : 2-16 d12-L1 : 18 Posterior surface: c4-s2 : 0-13 After examination of sensation: d6-d10 : 2-3 d12-L1 : 30		c4-d10 : 9-20 d12-L1 : 24 c4-s2 : 3-7	

* The following abbreviations are used: c, cervical segments of the skin; d, thoracic segments of the skin; L, lumbar segments of the skin; s, sacral segments of the skin, and V, face (area of the trigeminus nerve). The numbers in parenthesis indicate by how many millivolts the potentials of the hyperalgetic zone exceed those of the other parts of the trunk.

TABLE 2.—*Potentiometric Measurements of the Skin in Visceral Diseases with Referred Pain*—Continued*

Case	Name	Sex	Date	Diagnosis	Hyperalgetic Zone	Skin Potentials, Millivolts		Comment
						Left	Right	
15	N. J.	♂	1/25/33	Nephrolithiasis	No cutaneous hyperesthesia; spontaneous pain in left groin	V : 9 c4-L2 : 1-5	V : 3 c4-L2 : 1-7	10% sodium chloride
16	P. G.	♂	4/24/34	Duodenal ulcer	d7-12 (right) d10-12 (left)	V-d2 : 0 d4 : 12 d7 : 15(+3) d8-10 : 9 d11-12 : 4 L2 : 12	V-d6 : 2-3 d7 : 9 d8-9 : 10 d9-10 : 16.5(+13) d11-12 : 12 L2 : 9	
17	P. M.	♀	2/20/34	Cholelithiasis	c4:d7-9 (right)	Anterior surface: V-L2 : 0-5 Posterior surface: c4-s2 : 13-20 Only d6-7 : 28 d10 : 22	V-L2 : 0-2 Only c4: 7 c4-s2 : 2-13 d10 : 22	
18	R. R.	♀	5/12/34	Nephrolithiasis	Anterior surface: d11 (left) Posterior surface: d9-11 (left)	c2-L2 : 0-4 d10-12 : 6(+4) Rest of trunk : 0-2	c2-L1 : 0-4 c4-s2 : 0-3	
19	R. M.	♂	12/19/33	Nephrolithiasis; sigmoiditis	d12-L1 right > left	Anterior surface: c4-d9 : 7-13 d10-12 : 16 d12-L1 : 17(+4) L3 : 13 Posterior surface (median line): c4-d6 : 0-3 d8-9 : 16 d11-12 : 47(+31)	c4-d11 : 0-3 (Only perumbilical : 15) d12-L1 : 18(+3) L3 : 3 d12-L1 : 24(right) d12-L1 : 31(left) s2 : 12	On the back measurement only in median line possible on account of intensive growth of hair
20	S. R.	♂	2/25/33	Duodenal ulcer	d8-10	V-d12 : 1-3 Only d7-8: 7 d8-9 : 14(+11)	V-d12 : 1-5 Only d7-9: 9(+4)	
21	S. A.	♂	2 25/33	Gastric ulcer	d8 (left) and c4 (only very slight hyperalgesia)	V-d12 : 4-5 Only c4-d2 : 12.5	V-d12 : 1-5 Only d9-10 : 7	

22	V. F.	♂	2/ 1/33	Gastric ulcer; inguinal hernia	d8-d12 (maximum d12, right > left)	V-c4 : 1 d6-10 : 5 d12 : 8 L2 : 5	V : 9 c4 : 7 d6 : 11 d8 : 9.5 d9-10 : 11.5 d12 : 14.5(+3) L2 : 11	10% sodium chloride
23	W. M.	♂	2-21/33	Nephrolithiasis (acute pain)	d12-L1 (bilateral)	V-L1 : 0.5-1	V-L1 : 1-3	10% sodium chloride
24	W. R.	♀	2/21/33	Nephrolithiasis 3 years ago	No	V-d12 : 0-7	V-d12 : 1-9	
25	L. M.	♂	3/22/32	Coronary pain	No hyperalgesia; only slight pain on left side of chest	V : 21 d2-6 : 8(+2) d8-12 : 6	V : 27 d2-6 : 11 d8-12 : 13	
26	L. W.	♂	3/24 32	Coronary thrombosis	Maximum: d2-d4 (left) d6-12 (slight, left)	V : 35 d2-6 : 40(+9) d8-L2 : 29-31	V : 28 d2-6 : 37(+4) d8-L2 : 24-33	
27	P. W.	♂	1/23/34	Coronary sclerosis	Uncertain (d3-4)	V : 12 c4 : 16 d4 : 10 d8 : 21(+14) d9 : 18 d10 : 7 d12 : 2 L2 : 7	V : 12 c4 : 4 d4 : 0 d8 : 4 d9-12 : 0-3 L2 : 11	Patient under morphine (⅙ grain [11 mg.] every 3 hours)
28 (fig. 2)	S. J.	♂	3/24/32	Angina pectoris	c8-d4 (left)	V : 24 d2-4 : 31(+22) d9-12 : 0-9 L2 : 17	V : 18 d2-4 : 32(+18) d9-12 : 7-14 L2 : 13	
29	S. A.	♂	4/25/34	Coronary thrombosis	No	d8 : 16.5(+3) Other parts of trunk : 5-13	d2-4 : 20(+13) Other parts of trunk : 0-7	
30	S. O.	♀	4/25/34	Coronary thrombosis	d2-3 (slight, left)	c4 : 10 d2 : 27(+22) d4-5 : 18 d8-12 : 0-5	d4-5 : 18(+18) Other parts of trunk : 0-8	
31	Z. M.	♂	12/ 1/32	Coronary pain	d6-8 (left)	V : 2 c4 : 23 d4 : 49(+34) d6 : 37 d10 : 11 d12 : 15	V-d12 : 2-8	
32	Z. T.	♂	2/23/34	Coronary sclerosis	c4-d4 (left) c4-d2 (right)	c4 : 7 Face and rest of trunk : 0-3	c4 : 9 Face and rest of trunk : 0-5	

and Flockenhaus [7] and by Keller [6] in their studies of these potentials in conditions other than those investigated by us. We are here interested particularly in the potentials obtained on the trunk, because pathologic changes of the potentials in visceral diseases are found in this region. The highest values obtained in the dermatomes of the trunk in our control subjects were, as a rule, below 30 millivolts. In one case only (no. 7) a value of 31 millivolts was obtained around the umbilicus. The patient, G. R., who was obese, received 3 grains (0.195 Gm.) of thyroid daily. We found in other studies that this substance may increase the potentials of the skin. On the face, values up to 35 millivolts were obtained; from the palms and the soles even higher potentials could be led off.

In cases of visceral pain, as already mentioned, the regions where pathologic vegetative innervation of the skin is to be expected are mainly localized on the trunk, so it is often sufficient to limit the comparison of the potentials to the dermatomes of the trunk only. We considered high values that were obtained on the face or on the limbs to be pathologic only when the neighboring dermatomes of the neck and trunk showed an increased value. In other words, a high potential of the face or limbs as well as of the trunk indicated an irritation of a continuous series of spinal segments. Munk mentioned, rightly, that even in normal persons the values are sometimes irregular around the nipple and high around the umbilicus. In cases of such irregularities it is advisable to make the measurements in more lateral parts of the body, e. g., in the anterior axillary line.

The potentiometric measurements of the skin for patients with visceral disease and referred pain are shown in table 2 and in figures 1 and 2.

Hyperalgetic zones were found in twenty-five of the thirty-two patients with visceral pain. A comparison of the potentials of the patients with referred pain with those of the control subjects shows that the potentials of the hyperalgetic zones for ten patients exceeded 30 millivolts (figs. 1 and 2), the maximum value normally found for the dermatomes of the trunk. But even if the potentials led off from the hyperalgetic areas remain below 30 millivolts, the abnormal excitation of the vegetative elements in these dermatomes can be revealed if the potentials are compared with those of the remaining parts of the trunk. While three of the twenty-five patients showed no abnormal potentials, for thirteen cases the potentials of the hyperalgetic zones exceeded the maximal potentials on the other parts of the trunk by more than 10 millivolts (for five of the thirteen patients by from 20 to 30 millivolts

7. Munk, F. M., and Flockenhaus, M.: Ztschr. f. d. ges. exper. Med. **61**:363, 1928.

and for three by more than 30 millivolts). The potentials of the hyperalgetic zones for the remaining nine patients exceeded those of the other dermatomes of the trunk by less than 10 millivolts. It seems advisable to consider the reactions in the latter group as doubtful with the exception of those obtained for such patients as L. W. (case 26) for whom higher maxima than those obtained for the control subjects (more than 30 millivolts) were led off from the dermatomes of the trunk. The increased potentials are sometimes demonstrable on both sides in the

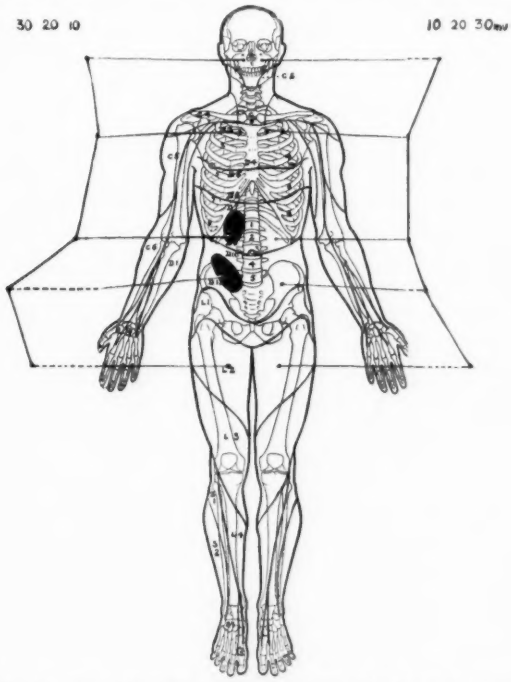

Fig. 1 (L. M., case 11).—Hyperalgetic zones (black) and potentials of the skin (in millivolts, represented by the abscissas of the graphs) in a case of duodenal ulcer.

respective segments, although the hyperalgesia is only unilateral (e. g., L. W., case 26; S. J., case 28 [fig. 2]).

Mechanical stimulation of the skin as used in examination of pain sensibility by pinprick can increase the potentials of the hyperalgetic zones (case 14, B. M.), while the potentials of the other dermatomes may remain low. As a rule, however, we studied the viscerogalvanic reaction before the examination of sensation. For two of the seven patients without cutaneous hyperalgesia, potentials were obtained on

the dermatomes corresponding to the diseased organs which exceeded those obtained on the rest of the trunk by more than 10 millivolts (C. A., case 3; S. A., case 29), and values above 30 millivolts were reached for B. F. (case 2) and C. A. (case 3). These observations show that the examination of the potentials in visceral diseases sometimes permits the localization of the corresponding segments, although the examination of the sensation fails to give such a localization. In this regard, case 27 is of special interest. The patient, P. W., was suffering

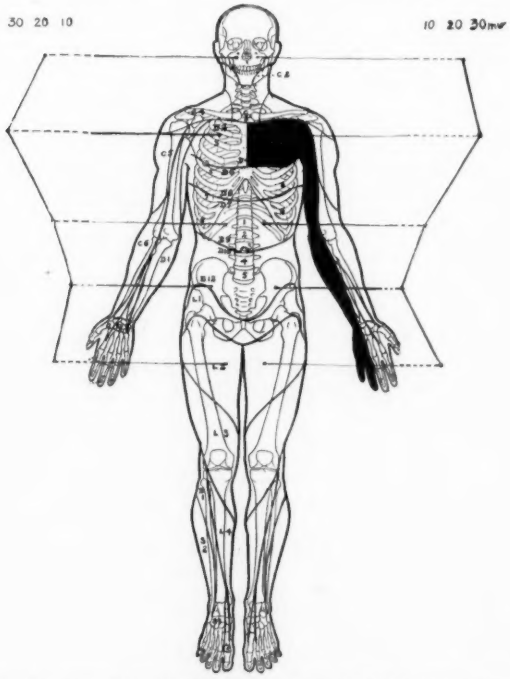

Fig. 2 (S. J., case 28).—Hyperalgetic zones (black) and potentials of the skin (in millivolts, represented by the abscissas of the graphs) in a case of angina pectoris.

from coronary thrombosis and was under the effect of morphine. He was therefore unable to localize the hyperalgesia; examination of the potentials, however, showed an increase in those of the left side of the chest. As morphine paralyzes the higher centers, where pain sensations enter consciousness, this observation indicates that the viscerogalvanic reaction can occur without the activity of these higher centers.

If one compares the area of hyperalgesia and the zone of increased potential, one may find in some cases that these two areas differ in their

extent and localization. This is to be expected if one considers the localization of the spinal centers of the sympathetic ganglions. It is known from the work of Gaskell,[8] Langley [9] and others that the preganglionic fibers of the sympathetic chain leave the cord between the eighth cervical and the second or third lumbar segment. These fibers supply the entire body with vegetative impulses; the spinal centers of the vegetative elements of the skin of the body are limited, therefore, to segments between the eighth cervical and the second or third lumbar segment. It is apparent, then, that a certain segment of the cord supplies a much larger area of the skin with vegetative than with sensory fibers, as is shown in detail by the study of the pilomotor reflex (André Thomas [10]) and also of sweat secretion in diseases of the spinal cord (Foerster [11]).

If such a segment is in a state of hyperirritation due to increased stimuli from a visceral organ, the zone of hyperalgesia is to be expected to be smaller than the zone of increased potential, i. e., the zone of increased vegetative innervation of the skin. Likewise the differences between the location of the hyperalgetic zone and the areas of increased potential can be easily understood. To illustrate: The first thoracic segment supplies the ulnar side of the arm with sensory fibers, but it sends vegetative impulses not only to the arm but also to the neck and the head; consequently, hyperirritation of this segment might result in an area of increased vegetative innervation including the face. Indeed reflex stimulation of the cervical sympathetic nerve was observed in some cases of angina pectoris by Gibson,[12] Bittorf,[13] Conzen,[14] and Misch and Lechner.[15] This is in agreement with our observations on one of the patients (L. W., case 26) with angina pectoris, in whom the zone of high potential extended from the chest to the face, although the hyperalgesia was limited to the thoracic segments. In such cases of hyperirritation of the upper part of the thoracic segments the zone of increased vegetative innervation extends farther headward than the area of hyperalgesia. On the other hand, in cases of hyperirritation of the lower part of the thoracic segments or of the first two lumbar segments the zone of increased potential is to be expected to reach farther

8. Gaskell, W. H.: J. Physiol. **7**:1, 1886.

9. Langley, J. N.: The Autonomic Nervous System, Cambridge, England, W. Heffer & Sons, 1921.

10. Thomas, André: Le réflexe pilomoteur, Paris, Masson et Cie, 1921.

11. Foerster, O., cited by Guttmann: Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:1, 1931.

12. Gibson, G. A.: Brain **28**:57, 1905.

13. Bittorf, D.: Arch. f. klin. Med. **81**:65, 1904.

14. Conzen, F.: Ueber die periphere Sympathicusaffection insbesondere ihre Aetiologie und Symptomatologie, Leipzig, B. Georgi, 1904.

15. Misch, W., and Lechner, A.: Klin. Wchnschr. **8**:500, 1929.

caudally than the hyperalgetic zone. The first two lumbar segments of the cord, e. g., supply with vegetative fibers not only the corresponding dermatomes but also the skin from the tenth thoracic to the last sacral segment (Spiegel [16]).

In many cases hyperalgesia is found not in the whole extent of a dermatome but only in a relatively small part of it (fig. 1). Conceivably, in such a case only a part of the respective segment of the cord is in a state of hyperexcitation. It is easy to understand that under these circumstances only some of the vegetative elements of this segment are stimulated and that the zone of increased potential is also smaller than the area supplied from this segment with vegetative impulses. Thus, the viscerogalvanic reaction has a segmental distribution following the

TABLE 3.—*Potentials for L. W. (Case 26)*

Left	Skin Temperature, C.	Potential, Millivolts
Face	37.5	35
c4	35.9	..
d4	35.3	40
d8-9	35.3	29

TABLE 4.—*Potentials for L. M. (Case 11)*

Right	Skin Temperature, C.	Potential, Millivolts
d2-4	36.3	0
d8	36.5	9
d11-12	36.3	36

vegetative innervation of the skin by the respective segments of the spinal cord. The question arises as to which vegetative elements of the skin the viscerogalvanic reaction is to be attributed. Four groups of organs within the skin have to be considered: the vessels, the arrectores pili, the sweat glands and possibly the cells of the epidermis. In order to determine the eventual rôle of viscerovasomotor reflexes the temperature of the skin was measured in the various dermatomes in cases of referred pain in which the viscerogalvanic reaction was positive. It was found that different potentials may be led off from two areas that have the same temperature, e. g., the chest and the abdomen (tables 3 and 4).

This shows that the viscerogalvanic reaction does not depend on viscerovasomotor reflexes. Reflex contraction of the arrectores pili can also be excluded as a possible cause of the increased potentials, as the visceropilomotor reflex appears much more rarely than the viscero-

16. Spiegel, E. A.: Die Zentren des autonomen Nervensystems, Berlin, Julius Springer, 1928.

galvanic reaction; if the patient is examined, for instance in a warm room, the visceropilomotor reaction fails to appear despite a well developed viscerogalvanic reaction.

It may be inferred that the viscerogalvanic reaction is in relation to an increased activity of the sweat glands; this inference is strengthened by the fact that there exists also a close correspondence between the activity of the sweat glands and the galvanic response of the skin to psychic excitation (Darrow [17]). One can indeed find similarities in the two reactions. Both are more easily elicited with a warm skin; both show a decrease if the examination is repeated at short intervals. Ohm's resistance of the skin as measured with alternating currents is not changed in the galvanic response of the skin to sensory stimuli (Gildemeister [18]). We found, likewise, in the study of the viscerogalvanic reaction that the resistance of the skin measured with alternating currents may be the same in areas with quite different potentials (table 5). One should bear in mind, however, the possibility that nerve impulses

TABLE 5.—*Resistance of the Skin Measured by Alternating Current*

Area on Right Side	Resistance, Ohms	Potential, Millivolts
Face	3,600	26
c4	8,000	23
d4	6,500	28
d8-9	5,400	21
d11-12	5,700	26
L2	3,600	3

act not only on the sweat glands but also on the cells of the epidermis. This is applicable to the viscerogalvanic reaction as well as to the psychogalvanic reaction (Gildemeister [18]). To determine the eventual rôle of the epidermis in this phenomenon it will perforce be necessary to study the viscerogalvanic reaction in patients with congenital absence of sweat glands.

It should, however, be borne in mind that the galvanic skin response on psychic excitation (Tarchanoff's phenomenon) must be distinguished from the viscerogalvanic reaction; these two phenomena differ from each other mainly in two points: 1. While the Tarchanoff reaction usually affects the whole surface of the body and is normally due to stimulation of the higher and of the lower parts of the vegetative centers, the viscerogalvanic reaction shows a segmental distribution, indicating that mainly segments of the spinal cord are affected. 2. The Tarchanoff phenom-

17. Darrow, C. W.: J. Exper. Psychol. **10**:197, 1927.

18. Gildemeister, M., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1928, vol. 8, p. 765.

enon is a transitory reaction lasting a few seconds following a stimulus, while the viscerogalvanic phenomenon is a more or less continuous reaction, maintained by sustained impulses from the diseased internal organ.

SUMMARY

The electrical potentials of the skin as measured by the compensation method are often increased in areas which correspond to diseased visceral organs (viscerogalvanic reaction). This method can be employed as an objective means to demonstrate areas of referred pain.

EFFECT OF DIURETICS ON THE CARDIAC OUTPUT OF PATIENTS WITH CONGESTIVE HEART FAILURE

BEN FRIEDMAN, M.D.
NEW YORK

HARRY RESNIK JR., M.D.
NASHVILLE, TENN.

J. A. CALHOUN, M.D.
BOSTON
AND
T. R. HARRISON, M.D.
NASHVILLE, TENN.

Diuretic drugs are sometimes considered to be only of symptomatic value for persons with cardiac disease. Their beneficial effects in patients with pronounced dropsy are unquestioned, but minimal or latent edema is not generally considered as an important indication for their use.

Our own experience with diuretics has led us to believe that they possess much more therapeutic value than has been generally recognized. We have often observed amelioration of paroxysmal dyspnea, cough and other symptoms of cardiac failure, both in hospitalized and in ambulatory patients, following their use. This has occurred when no other change has been made in the therapeutic regimen and even when diuresis has been of slight degree.

We also gained the impression that the repeated use of diuretics in patients with minimal or latent edema tends to prolong life. With this in mind a group of case records were analyzed, and it was found that the patients who were treated vigorously with diuretics lived longer than nontreated patients with similar types of cardiac disease. However, since the patients were not rigidly controlled in regard to other therapeutic measures and since the number of cases was not sufficiently large to warrant statistical treatment, no definite conclusions could be drawn. Accordingly, we decided to make objective measurements of the effect of diuretics on circulatory and respiratory functions.

EFFECT OF THEOPHYLLINE ON VITAL CAPACITY

Observations were made on hospitalized patients who complained chiefly of dyspnea while at rest but who had either minimal pitting

From the Department of Medicine, Vanderbilt University School of Medicine.

edema or latent edema, as shown by loss of weight when diuretics were administered, without recognizable pitting. Their vital capacities were measured under standardized conditions before and after the administration of theophylline (chart 1). Ordinarily, patients who complain of dyspnea while at rest have slightly lower vital capacities in the evening than in the morning.[1] This tendency was noted in the subjects of the present study. However, on days when the patient received theophylline, the vital capacity was higher in the evening than in the morning in four of five comparisons. In eight of nine patients observed the level of the vital capacity seemed to be increased by the drug. The dif-

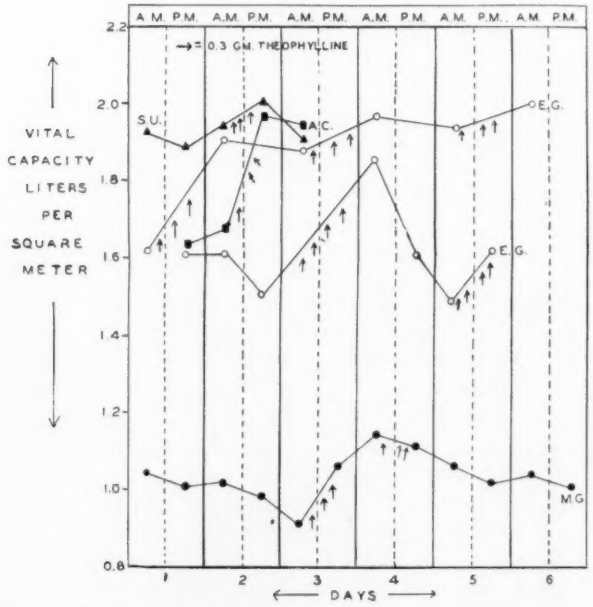

Chart 1.—Vital capacities of patients before and after the administration of theophylline.

ference was so slight as to be of questionable significance in several observations, but it was striking in others. In each of the patients

1. Harrison, W. G., Jr.; Calhoun, J. A.; Marsh, J. P., and Harrison, T. R.: (*a*) Studies in Congestive Heart Failure: XIX. Reflex Stimulation of Respiration as the Cause of Evening Dyspnea, Arch. Int. Med. **53**:724 (May) 1934; (*b*) The Cisternal Pressure in Congestive Heart Failure and Its Bearing on Orthopnea, ibid. **12**:1075, 1933; (*c*) Cerebrospinal Fluid Pressure and Venous Pressure in Cardiac Failure and the Effect of Spinal Drainage in the Treatment of Cardiac Decompensation, ibid. **53**:782, 1934.

whose vital capacities are recorded in chart 1, there occurred a slight diuresis, the body weight declining from ½ to 2½ pounds (from 0.25 to 1.1 Kg.) on the day theophylline was administered. Each patient was improved by the drug, although most of them complained of the nausea induced by it.

In presenting these results we deliberately have chosen patients who exhibited improvement in dyspnea with minimal diuresis. When patients are more edematous and striking diuresis occurs, there is frequently an associated amelioration of dyspnea of more marked degree.

The reason for the clinical improvement following minimal diuresis has been a subject of further study. Loss of pulmonary edema may be responsible in some cases but can scarcely be the sole factor, because relief of dyspnea may occur in persons who have no râles in the lungs. It is possible that decrease in spinal fluid pressure,[1b] and diminution in volume of blood due to concentration of the blood may each play a rôle, but these possibilities have not been studied. Our attention has been centered rather on possible alterations in the state of the circulation as a result of diuretics.

EFFECT OF THEOPHYLLINE AND OF SALYRGAN ON THE CARDIAC OUTPUT AND RELATED FUNCTIONS

Measurements have been made of oxygen consumption (by analysis of the expired air), of arteriovenous oxygen difference (using the three sample acetylene technic) and of cardiac output, vital capacity, ventilation, body weight and heart rate before and after the administration of diuretics. All of the patients were hospitalized and studied while in the basal state. The details of the methods used have been presented in previous papers.[2] Since the method of measuring the cardiac output is difficult to apply to persons with severe congestive heart failure, most of the persons chosen for the study had only slight edema. They were all well accustomed to the procedures, and none of them displayed undue anxiety or apprehension.

The results are shown in table 1. Following the administration of a diuretic the patient lost 1 or more pounds of weight within twenty-four hours in eleven of twelve observations. In most instances the patient stated that the degree of dyspnea was diminished. Well marked increase in vital capacity occurred in five instances, slight increase in five, and no change in two. The quotient $\frac{\text{Ventilation}}{\text{Vital Capacity}}$ was diminished

2. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**:751, 1933. Friedman, B.; Clark, G.; Resnik, Harry, Jr., and Harrison, T. R.: Effect of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure, Arch. Int. Med., to be published.

TABLE 1.—*Effect of Diuretics on the Circulatory and Respiratory Functions of Patients with Congestive Heart Failure*

Subject	Diagnosis	Date, 1933	Dyspnea*	Edema	Body Weight, Pounds	Vital Capacity, Liters	Ventilation: Vital Capacity	Heart Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Comment
G. S.	Hypertension; auricular fibrillation	8/ 8	+++	+++	212	1.50	7.40	..	366	96	3.81	Before treatment
		8/ 9	++	++	196	1.50	6.68	..	319	86	3.72	After 2 cc. of salyrgan
A. M.	Syphilitic aortic insufficiency	8/25	++	+++	160	2.60	3.77	73	290	114	2.55	Before treatment
		8/26	+	++	150	2.90	3.71	81	278	118	2.36	After 2 cc. of salyrgan
		9/ 1	++	+	143	3.25	2.66	64	224	105	2.12	Before treatment
		9/ 2	+	0	136	3.30	2.62	68	232	132	1.76	After 2 cc. of salyrgan
A. T.	Mitral stenosis	7/29	++	++	95	1.75	5.60	..	185	100	1.85	Before treatment
		7/31	+	+	89	1.85	5.30	..	187	71	2.62	After 1.5 cc. of salyrgan
C. M.	Syphilitic aortic insufficiency	8/ 3	++	+	133	2.10	5.92	56	201	73	2.74	Before treatment
		8/ 5	+	0	130	2.50	4.26	56	206	79	2.61	After 2 cc. of salyrgan
E. P.	Mitral stenosis; auricular fibrillation	5/ 3	+	+	124	1.68	3.68	52	193	76	2.55	Before treatment
		5/ 5	±	0	117	1.85	3.08	54	192	77	2.48	After 2 cc. of salyrgan
L. W.	Mitral stenosis; auricular fibrillation	11/3	+	+	125	2.95	1.74	52	161	77	2.10	Before treatment
		11/4	+	+	124	3.10	1.70	52	168	80	2.09	After 2 cc. of salyrgan
G. M.	Syphilitic myocarditis	9/18	+	±	132	2.20	4.64	72	225	91	2.48	Before treatment
		8/20	+	±	130	2.20	5.04	74	253	75	3.37	After 1.5 Gm. of theophylline daily for 2 days
L. M.	Hypertension	3/25	++	±	160	2.35	3.31	85	264	94	2.81	Before treatment
		3/27	++	±	159	2.50	3.06	88	262	95	2.76	After 1.5 Gm. of theophylline
L. W.	Mitral stenosis; auricular fibrillation	6/28	+	0	114	3.10	2.50	64	202	63	3.21	Before treatment
		6/30	0	0	116	3.55	2.46	84	213	68	3.13	After 0.9 Gm. of theophylline daily for 2 days
		8/12	+	±	119	3.10	2.82	80	212	83	2.55	Before treatment
		8/15	0	±	118	3.40	2.49	76	217	75	2.90	After 0.9 Gm. of theophylline daily for 2 days
		2/28	++	++	127	2.70	3.06	68	228	78	2.91	Before treatment
		9/ 1	+	+	122	3.00	1.98	68	210	70	3.01	After 0.9 Gm. of theophylline daily for 2 days

* The symbols +, ++ and +++ indicate, respectively, dyspnea on exertion only, dyspnea on exertion with slight dyspnea at rest and dyspnea on exertion with moderate dyspnea at rest.

significantly by diuretics in seven of twelve observations and was increased in only one. Consistent changes in heart rate and oxygen consumption did not occur. The cardiac output per minute was increased in three observations, decreased in one and unchanged in eight. (Changes in this function of less than 10 per cent are not considered as significant.) In proportion to the metabolism, the cardiac output following the administration of diuretics was greater in five observations and less in one. No correlation existed between the changes in the cardiac output and the degree of clinical improvement.

Since significant changes in the cardiac output did not occur in eight of the twelve observations, one might be inclined to attribute the changes found in the four other instances to error. However, this is unlikely, for the method used to measure the cardiac output permits one to detect fallacious results, and the rather rigid criteria which were used were adequately fulfilled in those instances in which well marked changes in the cardiac output occurred. Another explanation for the results obtained is that diuretic drugs have two different actions, the one tending to increase and the other to decrease of the output of the heart. In order to study this possibility additional observations were made.

Two patients who exhibited fluctuations in the cardiac output following the administration of diuretics were studied over a period of several weeks, no therapy being employed other than diuretic drugs, sedatives when needed and digitalis, the daily dose of which was kept constant. Observations on one of these patients during three successive "breaks" are shown in chart 2. In May, diuresis was associated with a slight increase in the cardiac output in proportion to the metabolism, as shown by a decrease in the arteriovenous difference, although the actual cardiac output declined. In June, diuresis was associated with an initial increase, followed by a marked decrease, in the arteriovenous difference. When, in July, diuretics were withdrawn and the patient was given an abundance of fluids, reaccumulation of edema was associated with an increase, followed by a decrease, in the arteriovenous difference. Diuresis was again accompanied by a decrease, and then by an increase, in the cardiac output in proportion to the metabolism. (In this man, who has repeatedly shown a marked increase in oxygen consumption during congestive heart failure, the arteriovenous difference is more reliable than the cardiac output as an index of the blood supply to the tissues.) The alterations depicted in chart 2 are compatible with the idea that two opposing factors, the one tending to increase the blood supply to the tissues and the other tending to have the reverse effect, are acting on the vascular system when edema is gained or lost.

In an attempt to distinguish between the possible peripheral and cardiac actions of diuretics, observations have been made of the oxygen utilization of the blood passing through the legs. Following the usual

measurements of the oxygen consumption and of the arteriovenous oxygen difference, samples of blood were drawn from the femoral vein and from the brachial artery. Analyses of the oxygen content were then made with the Van Slyke manometric apparatus. These observations are shown in charts 3 and 4. In one subject (chart 4), the oxygen utilization as determined on blood from the femoral vein first decreased and then steadily increased as diuresis occurred. The other patient

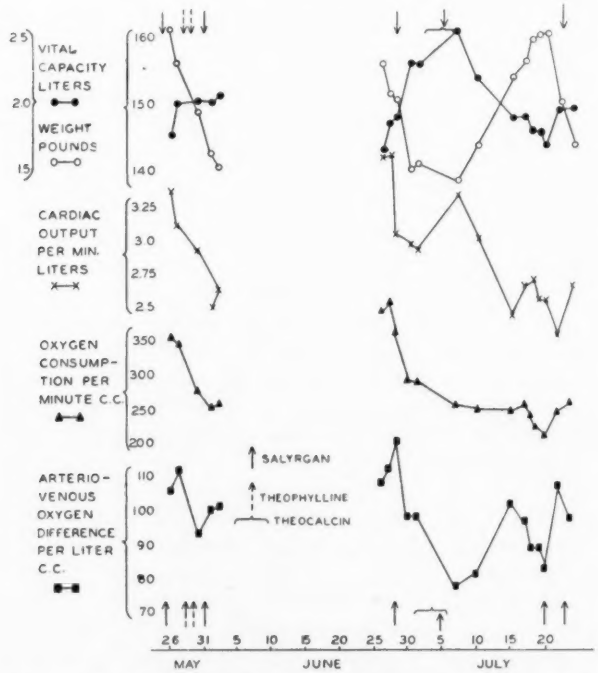

Chart 2.—Fluctuations in cardiac output following the administration of diuretics to a man (F. B.) with syphilitic aortic insufficiency.

(chart 3) likewise exhibited an increase in the arteriovenous oxygen difference of the blood passing through the leg as edema decreased. One of the patients had a striking decline in the general oxygen utilization; the changes in this function were inconstant in the other patient. Both patients exhibited a marked increase in the arteriovenous oxygen difference of blood from the femoral vein as compared with the general arteriovenous oxygen difference. These results indicate that in proportion to the metabolism a greater proportion of the blood pumped by the heart passed through the legs when edema was present than when

it was absent. These results are similar in general to those reported by Harrison and Pilcher.[3] Our actual values for oxygen utilization in the legs are considerably greater than theirs. Probably this difference is to be attributed to the conditions under which the observations were made. Their patients were studied while semirecumbent in bed; ours were sitting upright in wheel chairs. As compared with the other tissues of the body, it appears that edematous tissues have a relatively great blood supply. One effect of diuretics, then, is to tend to diminish the

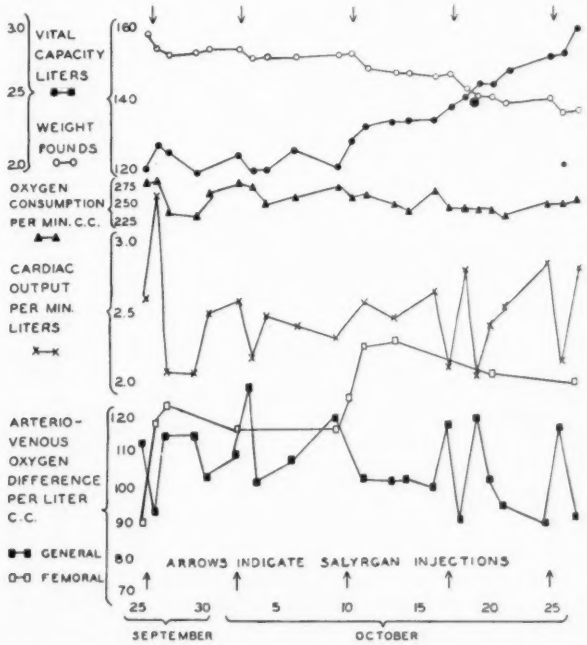

Chart 3.—Increase in the arteriovenous oxygen difference of the blood passing through the leg as edema was lost following injections of salyrgan in a man (F. B.) with syphilitic aortic insufficiency.

flow of blood through the edematous tissues. If other conditions remain constant, such an action will tend to decrease the cardiac output. The diminution in cardiac output and the increase in arteriovenous oxygen difference which sometimes follow the administration of diuretics are probably related to a peripheral effect secondary to loss of edema (table 1 and charts 3 and 4).

3. Harrison, T. R., and Pilcher, C.: Studies in Congestive Heart Failure: I. The Effect of Edema on Oxygen Utilization, J. Clin. Investigation **8**:259, 1930.

Such a conception may account for a decline in cardiac output but does not explain the increase in this function which occurred following diuresis in many instances (table 1 and charts 3 and 4). With a constant pulse rate, the output of the heart may become greater either because of an augmented venous return or as a result of an increase in the contractile power of the heart. In our studies venous pressure was not measured, and hence we are unable to state with certainty that peripheral factors were not responsible for the increase in cardiac output. However, this seems unlikely on a priori grounds; furthermore,

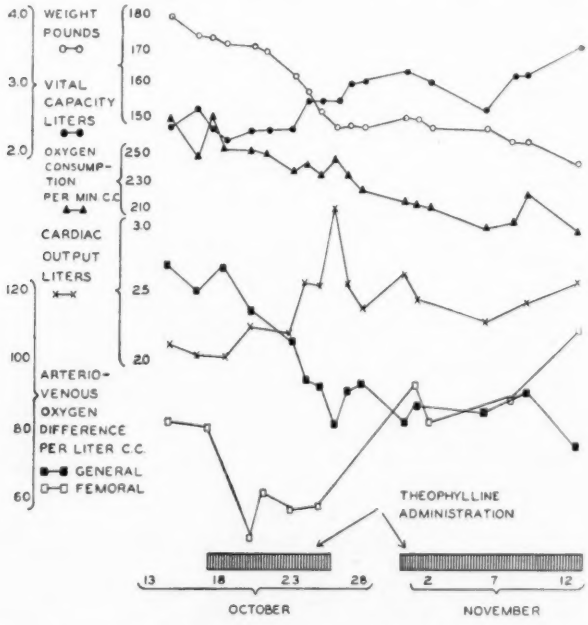

Chart 4.—Decrease and then increase in oxygen utilization as determined on blood from the femoral vein as diuresis occurred following injections of theophylline in a patient (A. M.) with syphilitic aortic insufficiency.

Harrison [4] found that the venous pressure of persons with congestive heart failure often, although not always, diminishes following the administration of diuretic drugs. Is it likely, then, that the rise in cardiac output is dependent on an increase in the contractile power of the heart? In the case of theophylline such an action might be the result of the augmentation of the coronary flow of blood which is produced by the xanthine group of drugs. However, there is no evidence that salyrgan,

4. Harrison, W. G., Jr.: Personal communication.[1e]

which may cause an increase in the output of the heart when it produces diuresis (chart 3), has any action on the coronary flow of blood.

Another possible explanation for the increase in cardiac output which has sometimes been observed after the administration of diuretics is as follows: Nielson and Palm [5] found that a frog's heart, which following artificial perfusion had begun to fail, was restored by perfusion with blood serum. Since no beneficial effects were observed when an ultrafiltrate of serum was used, it was believed that the restorative action of serum was dependent on its proteins and was brought about by withdrawal of water from the cardiac muscle into the perfusing fluid. It is well known that persons dying of congestive heart failure often exhibit myocardial edema. The water content of the heart in such conditions often is increased and the content of solids correspondingly diminished (table 2). It is conceivable that diuretic drugs may

TABLE 2.—*Content of Solids of the Right and Left Ventricles of Persons Dying With Congestive Heart Failure and of Persons Dying Without Cardiac Disease*

Authors	Number of Patients Studied		Content of Solids of Right Ventricle, Percentage				Content of Solids of Left Ventricle, Percentage			
		Patients	Control Patients		Cardiac Disease		Control Patients		Cardiac Disease	
	Control Patients	with Cardiac Disease	Range	Average	Range	Average	Range	Average	Range	Average
Calhoun, Cullen, Clark and Harrison: J. Clin. Investigation **9**: 696, 1931	3	13	21.0 to 18.6	20.0	20.3 to 17.6	18.6	23.0 to 19.9	21.8	22.0 to 17.6	19.5
Wilkins and Cullen: J. Clin. Investigation **12**: 1063, 1933	5	8	23.1 to 18.8	20.8	21.8 to 16.4	18.5	22.0 to 19.9	21.1	21.1 to 17.9	19.5

reduce edema in the heart muscle and that such an action may make the heart a more efficient pump and so enable it to respond to a given venous pressure with a greater output. The latter change is significant, not from the standpoint of increased blood supply to the tissues, but as an indication of an increase in the reserve power of the heart.

The foregoing discussion may be summarized by saying that diuretics may possibly have a twofold action on the circulation: 1. Reduction of peripheral edema may be associated with a decrease in the flow of blood through edematous tissues in proportion to the metabolism. The resulting decline in venous return and in venous pressure tends to decrease the output of the heart. 2. Reduction of myocardial edema may lead to an increase in the contractile power of the heart and con-

5. Nielson, N., and Palm, D.: Beiträge zur Kenntnis der Bedeutung der Serumkolloide für die Herztätigkeit, Skandinav. Arch. f. Physiol. **55**:41, 1929.

sequent increase in output. The final result may be a rise, a fall or no change in cardiac output. The important point is that diuretic drugs appear to aid the heart by: (*a*) decreasing its load and (*b*) increasing its ability to carry the load. Either of these effects tends to produce benefit by diminishing the energy expended by the heart.

COMMENT

The chief therapeutic measures which are commonly employed in the treatment of chronic cardiac disease are rest and digitalis. Diuretics usually are reserved for the advanced stages when dropsy has become pronounced. The studies of the circulatory and respiratory functions which have been presented indicate, we believe, that diuretic drugs may be of considerable benefit to patients who have minimal or even indetectable edema. For a number of years we have employed them for this purpose, and the fact that they may have an effect on circulation appears to afford a rational basis for their use. Whenever rest, reduction of the intake of fluids, digitalis and sedatives fail to produce clinical improvement in patients with congestive heart failure, diuretic drugs, we believe, should be given a trial, even though there may be no obvious subcutaneous edema.

SUMMARY

Diuretic drugs, even when administered to patients with minimal edema, often produce marked relief from dyspnea. The vital capacity is frequently increased following their administration.

Constant effects on the cardiac output have not been observed following the administration of these drugs. Occasionally the output is diminished. This effect is believed to be due to loss of peripheral edema, for the blood supply of edematous tissues is, in proportion to their metabolic needs, often relatively greater than the blood supply to the tissues in general. In some instances the cardiac output is increased by diuretic drugs. This effect is believed to be dependent on an action of these drugs on the heart and possibly to be related to loss of edema from the cardiac musculature. In many instances the administration of diuretic drugs is followed by no demonstrable change in the cardiac output. In such instances it is believed that the peripheral and cardiac actions of the drugs tend to neutralize each other. In favorable circumstances diuretic drugs appear to cause benefit both by tending to decrease the load on the heart and by increasing the ability of the heart to carry its load.

The foregoing evidence is interpreted as indicating that diuretic drugs are of more than symptomatic value. They should be employed frequently for ambulatory patients who have minimal edema or who are suspected of having latent edema.

TEACHING MEDICAL STUDENTS OBJECTIVES FOR CARE OF PATIENTS AND SOCIAL ASPECTS OF ILLNESS

ETHEL COHEN, M.S.
AND
HARRY A. DEROW, M.D.
BOSTON

It is the effect upon him [the patient] singly or collectively, which is the final test of the worth of any and every part as well as the whole of medical science. In the crowded times of new discoveries and of the development of more and more accurate means of diagnosis, we may perhaps find our excuse in having forgotten the object of it all—the patient himself. However that may be, the fact is, that from about the time of Lister to almost the present day, forgotten he has been. During this period, the study of disease, not of patients, has been the object of most of our best endeavor. But now the rediscovery of the patient as the most important item in the picture has changed all that, and the new generation of physicians can now, at the very beginning of their careers, go forth with the brand new but very old fashioned and sane objective of helping their patients to avoid illness, to overcome illness, or failing this, to die with as little suffering as possible. To this end, scientific methods, the laboratories, and all other means become the ready servants of the art of medicine. But the Art itself will be blind unless it is guided by an understanding of the individual patient and, furthermore, of the significance to him both of his illness and of his treatment.[1]

Although this ideal is ably expressed by Dr. Riggs and shared by many leaders of the medical profession,[2] in general, insufficient consideration is given to the total needs of the patient. This is due to the tendency to plan only in terms of the present situation without taking a long-range view of the entire problem. Impersonal stereotyped advice for a change of regimen is frequently given without regard to the social elements which may render such advice entirely impracticable. To overcome this defect a plan[3] known as "Medical Social Ward Rounds" was evolved at the Beth Israel Hospital to train young physicians during their internship. Because of the contribution of this

From the Medical and Social Services, Beth Israel Hospital.

1. Riggs, A. F.: The Significance of Illness, in Emerson, L. E.: The Physician and Patient, Cambridge, Mass., Harvard University Press, 1929, p. 101.

2. (*a*) Edsall, D. L.: Some of the Human Relations of Doctor and Patient, in Emerson, L. E.: The Physician and Patient, Cambridge, Mass., Harvard University Press, 1929, p. 3. (*b*) Minot, G. R.: The Physician, Student and Social Worker, Boston M. & S. J. **193**:1090 (Dec. 10) 1925. (*c*) Means, J. H.: The Social Component in Medicine, Hosp. Social Serv. **24**:74, 1931.

3. Derow, H. A., and Cohen, E.: The Training of Interns in the Social Aspects of Medicine, New England J. Med. **209**:827 (Oct. 26) 1933.

procedure to the development of the intern it was believed that it might be profitable to the student to give him a similar type of experience during his period as an undergraduate in the medical school.

For a number of years the teaching of the social implications of disease has been developing.[4] Since the opening of the Beth Israel Hospital in 1928 several different methods have been tried and discarded. In 1933 and 1934 an entirely new plan of teaching was developed, and that plan is being reported at this time because of its effectiveness in stimulating the students' interest. It consisted in correlating the purely medical aspects of a disease with an interpretation of the significance of the disease and its treatment in the life of the individual patient. In addition, especial emphasis was placed on the formulation of specific objectives for the care of patients.

OUTLINE OF PLAN

Scope of Teaching.—Seminars lasting from two to two and one-half hours were conducted jointly by a medical instructor and a medical social worker in an office of the hospital. Successive groups of from three to nine students of the fourth year classes of Harvard University Medical School and Tufts College Medical School participated. Each student from Harvard University Medical School attended four sessions, and each student from Tufts College Medical School attended only two sessions because of the shorter period of assignment at this hospital. Fourth year students were chosen rather than third year students because the clinical training which students received in the third year served as a preparation for this type of analysis and evaluation.

Each seminar included (1) a review of the medical aspect of a certain disease, (2) a discussion of general objectives for the care of patients with the disease under consideration, (3) the presentation of several patients with the disease under consideration, (4) a discussion of the specific means of achieving the objectives outlined and (5) a recapitulation of the salient factors.

Instructors' Preparation for Seminars.—Each seminar required considerable advance collaboration and preparation by both instructors. The choice of diseases, the selection of patients, the study of records and an outline of the material to be presented were made jointly. Arthritis, asthma, carcinoma, cardiac disease, peptic ulcer, rheumatic infection and tuberculosis were discussed. Two or three patients were selected from the ward and from the medical instructor's private practice to illustrate the various types of problems found in a certain disease

4. Cannon, I. M.: Teaching Medical Students the Social Implications of Illness, New England J. Med. **211**:216 (Aug. 2) 1934. Minot.[2b]

in both its chronic and its acute aspects. Patients from private practice were included to demonstrate that these problems exist not only in hospital wards but also in private practice, regardless of the patient's social or economic status.[5]

After the patients had been selected from the ward each instructor read the medical records of which the social history prepared by the student was a part. The medical instructor also made his own examination of the patients. The social situation and the possibilities for executing the medical recommendations were ascertained from the social worker's record and from visits to the patient's home made by a social worker.

After the records had been studied and before the opening of the seminar an outline was prepared jointly by the instructors to insure continuity in presentation of the subject matter. Decisions were then made as to the subjects in the outline which each instructor would present. The instructors prearranged the questions which they would ask the students during the seminar for the purpose of stimulating general discussion. It was agreed that the medical instructor would assume responsibility for essentially medical questions and the social worker that for questions on social aspects. Each instructor was expected to supplement the remarks of the other. It was planned to encourage the students to raise questions and to make comments at all times during the seminar, even if the instructors' planned presentation was interrupted.

METHOD OF PROCEDURE

A typical seminar was conducted in the following manner:

1. *Review of the Medical Aspect of the Disease.*—The medical instructor presented a review of a specified disease. This included a discussion of the etiology and of methods of establishing a diagnosis, the presentation of an outline of the natural course of the disease and a discussion of the method of estimating the prognosis for the duration of life and the amount of activity that might be permitted with and without treatment. During this review of the medical aspect of the disease the medical instructor by direct questioning sought every opportunity to foster the students' participation.

2. *Discussion of Objectives for the Care of the Patient.*—After the review of the medical aspect of the disease there was a discussion of objectives for the care of patients with the disease. The objectives which had particular application to the disease under consideration were selected from the following list: (1) to restore the patient to complete health, (2) to restore the patient to the usual state of health, (3) to pre-

5. Minot, G. R.: Medical Social Aspects in Practice, Arch. Int. Med. **54**:1 (July) 1934.

vent a recurrence of the disease, (4) to increase the patient's tolerance to the disease, (5) to effect a maximum amount of rehabilitation, (6) to arrest the progress of the disease, (7) to retard the progress of the disease and (8) to palliate an incurable progressive disease.

Restoration to complete health may be an impossible goal after an acute exacerbation of a chronic disease. The patient, however, may be restored to his usual state of health which, though impaired, may be the best state possible for him. There are times when the physician aims for more than one objective. For example, in the case of tuberculosis the immediate aim is to arrest the progress of the disease. A second aim is to restore the patient, if possible, to complete health. A third aim is to prevent recurrence of the disease in the patient, and another, broader, aim is to prevent its spread in the community. In cases of chronic arthritis the aims are to effect the maximum amount of rehabilitation, to arrest the progress of the disease and at the same time to increase the patient's tolerance to the disease.

It was demonstrated that the objectives for care also vary according to the stage of the disease at which the physician is making recommendations. For example, the aim in the care of a patient with an early stage of carcinoma of the breast would be restoration to complete health and prevention of recurrence, while in the case of a patient with a moderately advanced stage of carcinoma of the rectum the aim might be retardation of the progress of the disease. The only possible objective in a case of inoperable carcinoma of the stomach would be to palliate this incurable progressive disease.

After the discussion of objectives came the important question of the means to be used to bring about their achievement. It was shown how these objectives could be realized through utilization of the resources of the patient or of the community.

3. *Presentation of Patients.*—The general review of the medical aspect of the disease, the formulation of objectives and the consideration of the means of attaining them served as a background for the presentation of individual patients selected from the ward and from private practice because of their particular medical and associated problems.

The patients from the wards were well known to the students through the daily morning teaching visits. To save time the medical instructor, rather than the student, briefly outlined the history and present illness of one of these patients. The significant features of the case were graphically demonstrated by use of the patient's medical record and roentgenograms. A complete study of the case had already been made by one of the students. This included a consideration of the patient's racial background, emotional life, intellectual capacity, habits, attitudes, recreation and environment, economic status, occupation, facilities for after-care, etc.

After the instructor had presented the medical aspects the student who had studied the case described the patient's present condition and made recommendations for the patient's care. He was challenged by both instructors and by other students to state the basis for these recommendations. Objectives for the care of the individual patient were considered in the same way in which objectives had been discussed by the medical instructor in considering the disease entity. The social worker at this point asked how the recommendations could be carried out. First the student who studied the case proposed a plan. Then the other students either concurred in this plan or offered other plans. At this phase of the discussion came the opportunity for the social worker to point out the relationship between social factors and illness, in that the former are the cause of illness, a complicating element or the result of it.

For example, a student might make a recommendation for light work and freedom from emotional strain without realizing that the hypertensive patient for whom those suggestions were made was a mother of five small children, had burdensome household responsibilities and was in straitened financial circumstances. Similarly, the student might offer the simple suggestion of rest in bed for a patient with cardiac disease. In that case close inquiry by the social worker might reveal that the student had given no thought to the many elements involved for some persons in securing rest in bed. In a case in which rest in bed at home was impossible because of overcrowded housing and lack of necessary attention the student might suggest the alternative of placing the patient in a nursing home, a suggestion made without regard for the need of payment for such care, for the source of funds to provide it or for the methods by which such funds might be made available. A change to some light occupation might be proposed for an illiterate longshoreman incapacitated by infectious arthritis. Such change of occupation might be desirable, but the student failed to realize the futility of suggesting light work for an unskilled, middle-aged illiterate man, since it is usually impossible to find such work for a patient of this type. A blanket recommendation for placing the patient in a municipal sanatorium might be made for a tuberculous patient with disregard of the fact that if it were carried out serious problems would arise if the patient were a recent immigrant with no claim to governmental care, subject to deportation to a country from which he was a political refugee. The suggestion of a change of climate for a 40 year old rag-sorter, the head of a family of six, with severe bronchial asthma, might be made seriously with no consideration of obstacles involved, namely, the cost of transportation, maintenance in a strange, distant community, separation of the patient from his family and the support and management of that family.

In cases such as those mentioned the social worker with no information other than that provided by the student was sometimes able to demonstrate the nonfeasibility of the plan suggested because of her better correlation and more thorough interpretation of the data already known.

Why did the students fail to take all these facts into consideration? Was it because of the inadequacies of the histories that they had obtained? As a matter of fact, the histories were usually complete and accurate. The difficulties seemed to be due to the tendency to make the taking of the history a matter of routine unassociated in the students' minds with the realities confronting a certain patient, as well as to the failure to coordinate the facts gleaned during the taking of the history with the plan for treatment.

4. *Discussion of the Specific Means of Achieving the Objectives Outlined.*—In some cases a plan for after-care as suggested by the student was perfectly appropriate so far as the disease itself was concerned, yet was not practicable because of the student's failure to evaluate the individual patient's resources. In such cases the reasons for the impracticability of the plan suggested were pointed out by the social worker through her analysis of the data provided by the medical student and by her own investigation.

In some cases the student fully appreciated the inadequacy of the patient's resources but was unable to make a reasonable suggestion for future care because of his ignorance as to the existence of suitable community resources and the means of regimenting them in behalf of the patient.

The fourth part of the seminar included an explanation by the social worker that often the assistance of the department for social service of a hospital or of some other social agency is needed (1) to help patients analyze and evaluate their own resources and utilize them effectively, (2) to indicate to patients capable of self-direction the availability of community resources or (3) to execute for patients incapable of self-direction a plan of treatment which includes the use of community resources.

By discussing a certain disease in several patients, each of whom presented a different social situation, the various types of resources which might be needed were demonstrated.

The students were shown a copy of the "Physician's Handbook of Community Resources in Metropolitan Boston,"[6] which describes the medical, health and social resources available to patients in metropolitan Boston. As some students would practice in communities outside of

6. Physician's Handbook of Community Resources in Metropolitan Boston, published under the auspices of the Massachusetts General Hospital, Boston, 1933.

Boston it was suggested that they secure advice as to resources in their prospective communities from social service departments in hospitals or from local councils of social agencies.

The need for physicians to stimulate the development of additional resources, wherever such resources are lacking, was also brought out. The students took a lively part in this portion of the discussion, particularly the students from communities outside of Boston which are not highly organized from the point of view of social welfare.

The discussion of community resources led to a more general consideration of the responsibility of the community for the care of the sick and the economic cost of illness. Because of the diversity of their personal experiences and their philosophies of life, the students expressed a variety of opinions regarding (1) the patient's responsibility for meeting his own health needs, (2) the responsibility of relatives and employers, (3) the responsibility of the community for the care of the sick, etc. These opinions were discussed and evaluated by the two instructors, each contributing from the experience in his or her own field.

5. *Recapitulation of the Salient Factors.*—The seminar was concluded with a recapitulation by both instructors of the salient factors which had arisen in the consideration of the concrete problems of the patients discussed. The variation in plans for the treatment of different patients with the same disease was shown to be due to the factors of residence, racial background, religious scruples, emotional reactions, psychologic attitudes, intellectual endowment or any other component part of the social situation. The problems of patients from the wards were paralleled by the problems of the private patients of the medical instructor, and it was shown that, regardless of the more favorable economic and social status of private patients, the need still existed for adjustments of environmental, psychologic or emotional factors.[5]

The social worker reviewed in a general way the social implications of illness, the broad concept of the care of the patient rather than merely the treatment of a diseased organ. The medical instructor pointed out that it is important that the physician have clearly in mind what his objectives should be in the care of each patient, the value of appreciating and dealing with social obstacles that often prevent the achievement of these broad objectives and the need of calling on expert service in the community in various fields to assist in the attainment of his goal.

COMMENT ON METHOD OF PROCEDURE

The conferences were informal seminars conducted jointly by a physician and a medical social worker. Two seminars for each group seemed insufficient; four sessions gave more satisfactory results. It is

believed that six such meetings would afford greater opportunity to establish this type of thinking more firmly.

The teaching of the social component in illness, it was believed, could be handled best as a part of a medical exercise rather than as a separate isolated conference on social service. In preparing the outline and in conducting the seminar the instructors made a conscious effort to prevent devoting a disproportionate amount of time to the essentially medical discussion.

Experience demonstrated that the consideration of a single disease during one session of a seminar was more effective than the discussion of several diseases. The diseases which seemed to be of paramount importance, because of their incidence and their special medical and social implications, are arthritis, carcinoma, peptic ulcer, rheumatic infection, cardiac disease, syphilis and tuberculosis. These diseases, it is believed, should constitute the minimum considered by each group, although acute self-limited diseases present significant problems and should be included, if possible.

The students were asked to express their reactions to this experiment in teaching. There was general agreement that the review of the medical aspect broadened their concept of the disease itself by summarizing and unifying for them in a new way information which they had previously acquired in scattered parts of their curriculum. For the first time they realized that the presenting illness was only one episode in the natural history of a disease and that this episode as well as possible later complications had to be considered in making adequate plans for the care of the patient.

The discussion of objectives was an entirely new experience for the students, as they were obliged to voice their actual aims for the care of the patients. In the formulation of objectives for care and the planning of their achievement, special significance was necessarily placed on the patient and his needs rather than on the narrower concept of his disease. The students believed: (1) that a preliminary general discussion of a given disease served as a valuable background for the later presentation of concrete problems of individual patients with the same disease, (2) that such a discussion was a natural approach and conforms with their other clinical teaching and (3) that this method made the integration of the medical and social factors more effective and should permanently influence their future care of patients.

SUMMARY

A method of teaching medical students objectives for the care of patients and the social aspects of illness is presented.

The purpose was to demonstrate the need for physicians to give full consideration to the patient and his illness instead of placing exclusive emphasis on the disease.

The habit of giving such thought to patients may be established in medical students by the formulation of concrete objectives for the care of each individual patient and by the realization that to attain these goals the consideration of certain social and psychologic factors must be integrated into the whole process of medical study and treatment.

It is believed that the teaching of this subject should be carried on as a medical exercise conducted jointly by a physician and a medical social worker.

INCREASED EFFECTIVENESS OF INSULIN WHEN GIVEN BY INJECTIONS OF DOSES OF EQUAL UNITAGE AT INTERVALS OF TWO TO FOUR HOURS

I. USE OF INSULIN IN DIVIDED DOSES TO MANAGE SEVERE UNCOMPLICATED DIABETES AND TO CONTROL COMPLICATED MEDICAL CASES

BYRON B. CLARK, PH.D.

R. B. GIBSON, PH.D.

AND

WILLIAM D. PAUL, M.D.

IOWA CITY

The administration of insulin in divided doses, i. e., in injections of doses of equal unitage at two to four hour intervals day and night, was first used at University Hospitals in 1929 as an emergency postoperative measure. The results were sufficiently encouraging, and a further experimental study was made on 11 patients with uncomplicated diabetes in 1929-1930. These experiments indicated that insulin given in divided doses is much more efficient; that much less insulin is required; that the blood sugar level is more easily kept within satisfactory limits; that the glycosuria is more quickly controlled, and that hypoglycemic reactions rarely occur. The procedure has been of such great value that it has become a routine measure in managing severe uncomplicated diabetes which is difficult to control with two or three daily injections of insulin, in treating diabetes with associated acute infections and in handling postoperative cases. Of the 1,553 patients admitted to the diabetic service during the past five years, 146 have been treated with divided doses; 74 had severe uncomplicated diabetes and 72, complications, which were usually surgical.

METHOD

Either on admission or as soon thereafter as complications would permit the patients were placed on a maintenance diet of the Woodyatt type, e. g., protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm.—calories, 1,887. The diet was ordinarily kept constant during the period of hospitalization. Determinations of the blood sugar content [1] were usually made before the patient's admission to the hospital

From the Laboratory of Pathological Chemistry and the Department of Internal Medicine, University Hospitals, the State University of Iowa.

1. Gibson, R. B.: The Micro Determination of Blood Sugar, Proc. Soc. Exper. Biol. & Med. **27**:480, 1930.

and thereafter at 9 a. m., two hours after breakfast, and at other times as indicated. Twenty-four hour specimens of urine were examined daily for diacetic acid and sugar. The type of dosage of insulin as well as the amount depended on the diabetic and clinical condition of the patient.

Usually in uncomplicated medical cases an attempt was made to control the diabetes with the regular dosage of two or three daily injections of insulin. If after a few days with a reasonably high dosage of insulin the blood sugar level remained high or glycosuria persisted, a regimen of divided doses was instituted. In a number of cases regarded as experimental, a routine of divided doses was instituted after satisfactory management had been achieved in order to compare further the efficiency of the two types of dosage. Patients with acute infections were usually placed on a regimen of divided doses immediately on admission or at the time the infection developed. The length of the period of divided dosage varied from a few days to a month or even longer. Then the regular dosage was resumed. The treatment in cases of acidosis differed only in the initial stages of management, when repeated large doses of insulin were given intravenously with dextrose in physiologic solution of sodium chloride. As soon as the acute symptoms of the acidosis had subsided and the blood sugar reached a reasonable value, divided doses were started.

In surgical cases, except those requiring almost immediate operation, the condition was managed in the usual way, with diet and regular dosage of insulin. Two hours preoperatively the patient was given additional insulin and dextrose and divided doses were administered postoperatively whether he was able to take food or not. In the event of continued inability to ingest food and following certain surgical procedures, such as cholecystectomy, dextrose was given intravenously by hypodermoclysis or rectally either with or without additional insulin, usually depending on the condition of the patient, the amount of dextrose given and the mode of administration. When intravenous injections of dextrose were repeated over a period of several days, it was usually unnecessary after the first two or three injections to give additional insulin beyond that received in divided doses. These patients were usually given divided doses until they had recovered from the surgical procedure. In cases in which immediate operation was required, the initial procedure was to give insulin and dextrose intravenously, and divided doses were started immediately postoperatively.

Representative cases are described in detail in the accompanying case reports and tables.

RESULTS

We have uniformly observed that for patients with uncomplicated diabetes on a constant diet the requirement of insulin given in two or three daily injections can be reduced by as much as one third to one half when divided doses are given. Patients with a condition difficult to control responded satisfactorily on this regimen. It was of special interest to note that although the injections of insulin were given irrespective of meals the blood sugar level, while higher after breakfast, tended to decrease following the noon and evening meals and to be low during the night. However, in spite of the low blood sugar level which obtained at night, hypoglycemic symptoms were rarely encountered; reactions were more likely to occur during the day or early evening and were not so severe as those following large injections of insulin. To obviate the possibility of reaction, one injection, usually at midnight, was

omitted; but there were some cases in which it was necessary to include all the injections to keep the blood sugar level in the morning reasonable and the urine free from sugar. Patients treated with divided dosage remained resistant to hypoglycemic symptoms when the usual management was resumed. The tolerance of patients with severe uncomplicated diabetes tended to improve more rapidly (i. e., the insulin requirement was reduced) when given the divided dosage than when they received the usual type of dosage. On resumption of the regular dosage these patients required either the same amount of or, more often, more insulin. The gain in tolerance which they had shown while receiving divided doses was usually only in part sustained. Diet seems to be a factor in the success of the regimen of divided doses, as indicated by the fact that in some cases in which the diet was supplemented with an increased amount of carbohydrate there was a definite tendency to a lower requirement of insulin during the day and early evening than during the night and early morning. However, in a number of other cases in which a diet high in carbohydrate was used the use of divided dosage was satisfactory.

After surgical intervention patients for a time usually required larger amounts of insulin with divided dosage, but following recovery from the surgical procedure they usually showed such a marked improvement in tolerance that when regular dosage was resumed they required either the same amount of or, frequently, less insulin. The use of divided doses has been of exceptional value in carrying these patients through the postoperative crisis, and the postoperative course was usually uneventful and quite satisfactory.

Patients with complicated medical cases recovering from the acute stage of the disease had requirements of insulin similar to those of patients with surgical cases. The former required the same amount of or, more frequently, less insulin when the usual management was resumed after a regimen of divided doses. Control of their diabetes during the acute stage of the disease was much more satisfactory following the use of divided doses.

COMMENT

The data suggest a rather constant and continuous secretion of insulin on the part of the islet cells of the pancreas which would explain the increased efficiency of insulin given in divided doses.

Certain facts in the literature and common observations in the clinic for the treatment of diabetic patients indicate that such an explanation is rational. A direct relationship between the amount of insulin required to metabolize and store a definite amount of dextrose has not been satisfactorily demonstrated. A latency or long continued action of insulin has been observed in two respects: (1) the delayed or prolonged

effect of insulin which has been injected, and (2) a latent period in both the diabetic subject when deprived of insulin and the depancreatized dog before the development of maximal diabetes. Soskin and Allweiss [2] have demonstrated a normal curve for blood dextrose following the injection of dextrose into completely depancreatized dogs receiving a continuous intravenous injection of dextrose and insulin to maintain a constant blood sugar level. In such experiments they have also been able to show the hypoglycemic phase occurring at the end of the curve.[3] Recently Ellis [4] has shown a marked temporary improvement in tolerance in patients with severe diabetes by giving hourly administrations of insulin and dextrose. This improved tolerance, however, was not permanently sustained after the patients returned to their usual diets and regular dosage of insulin. Ellis also made one or two experiments in which hourly injections of insulin were used for patients on ordinary diets. The observations indicated an increased efficiency of the insulin with frequent injections. That the increased efficiency even in part is not accounted for by the excretion of some of the large doses in the urine is indicated by the failure to demonstrate the presence of insulin in the urine of such patients (Ellis,[4] Ueberrack and Zell [5] and the experiments of one of us [B. B. C.]).

One may assume, then, that the more or less constant and continuous secretion of insulin is adjusted to the habitual intake of carbohydrate. The effect of various diets on the dextrose tolerance has been shown by Sweeney [6] and has been confirmed repeatedly. Whether the ability to store and metabolize a supply of dextrose above the usual intake, as demonstrated in normal subjects by Hamman and Hirshman [7] and in diabetic patients by Gibson [8] in this hospital and by Ellis,[4] is due to

2. Soskin, S., and Allweiss, D.: Factors Determining the Dextrose Tolerance Curve, Am. J. Physiol. **105**:89 (July) 1933. Soskin, S.; Allweiss, M. D., and Cohn, D. J.: Influence of the Pancreas and Liver upon the Dextrose Tolerance Curve, ibid. **109**:155 (July) 1934.

3. Soskin, S., and Allweiss, M. D.: The Hypoglycemic Phase Following the Normal Dextrose Tolerance Curve, Am. J. Physiol. **109**:101 (July) 1934.

4. Ellis, Arthur: Increased Carbohydrate Tolerance in Diabetics Following the Hourly Administration of Glucose and Insulin Over Long Periods, Quart. J. Med. **3**:137, 1934.

5. Ueberrack, K., and Zell, F.: Ueber das Vorkommen von Insulin im Harn, Biochem. Ztschr. **239**:42, 1931.

6. Sweeney, J. S.: Dietary Factors that Influence the Dextrose Tolerance Test, Arch. Int. Med. **40**:818 (Dec.) 1927.

7. Hamman, L., and Hirshman, I. I.: Studies on Blood Sugar: IV. Effects upon the Blood Sugar of the Repeated Ingestion of Glucose, Bull. Johns Hopkins Hosp. **30**:306, 1919.

8. Gibson, R. B.: Latent Tolerance in Diabetes Mellitus: A Study of the Effect of High Sugar Diets with Insulin on Controlled Diabetics, J. Lab. & Clin. Med. **14**:597, 1929; Further Observations on Latent Tolerance in Diabetics, Proc. Soc. Exper. Biol. & Med. **26**:449, 1929.

an increased secretion of insulin is not clear. There is some evidence that this is the case; nevertheless stimulated glycogenesis must be an important factor in the mechanism of sugar consumption. The experiments reported in this paper lend considerable support to Macleod's idea that insulin produces a "sugar vacuum" in the tissues.

In view of these observations, the administration of insulin in divided doses is a rational procedure more closely approximating the normal physiologic mechanism, and hence one expects the requirement of insulin to be less and the patient's tolerance to improve faster than when insulin is given in the usual way. The experimental observations entirely confirm these theoretical considerations.

CONCLUSIONS

1. Contrary to the usual procedure insulin may be given in injections of amounts of equal unitage at intervals of from two to four hours day and night irrespective of meals.

2. Insulin given in this way is much more efficient.

3. The blood sugar value is somewhat higher after breakfast, lower following the noon and evening meal and quite low during the night. Hypoglycemic reactions rarely occur.

4. The data suggest a rather constant and continuous secretion of insulin by the islet cells of the pancreas.

5. In patients with severe uncomplicated diabetes the condition is more easily controlled and there is a more rapid improvement in tolerance with divided doses than with the regular dosage.

6. When the regular dosage of insulin is resumed, the patients with uncomplicated medical cases require either the same amount of insulin or, more often, more; those with surgical cases showing rapid recovery usually require the same amount but frequently less.

7. The use of divided doses is of great practical importance in treating patients with severe uncomplicated diabetes, those with acute infections and those recovering from surgical intervention.

REPORT OF CASES

CASE 1.—O. P. (table 1), a youth aged 16, was admitted to the hospital on March 4, 1930, with severe diabetes which began suddenly in 1927 and which had been controlled at home by diet and later with insulin. In January 1930 he had pneumonia, following which the intensity of the diabetes increased and he was referred to the medical service for management. His only symptoms were those referable to the diabetes. The physical examination gave essentially negative results.

On admission the blood sugar content was 460 mg. per hundred cubic centimeters. The patient was placed on a diet of protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm., equivalent to 1,887 calories. Regular insulin therapy was instituted at once. On March 10, the sixth day after admission, the diabetes was under

control, as judged by the blood sugar content and the diminished amount of sugar in the urine, with a dosage of 40 units of insulin before breakfast and 20 units before supper, a total of 60 units. On the following day he was given 4 units of insulin every two hours until ten injections were received (omitting the injections at 11 p. m. and 3 a. m.), making a total of 40 units. This resulted in a reasonable blood sugar value and the disappearance of sugar from the urine. On March 13, because of a reaction that evening, it was necessary to reduce the

TABLE 1.—*The Values for Blood Sugar in Case 1 with Insulin in Divided Doses*

Date	Urine Sugar	Blood Sugar, Mg.			Insulin Units		Comment
		9 A.M.	2 P.M.	7 P.M.	Dosage	Total	
3/ 4/30	...	...	460	...	-20	20	
3/ 5	4+	306	...	...	25-10-20	55	
3/ 6	—	281	...	...	30-10-20	60	
3/ 7	4+	241	...	...	40-10-20	70	
3/ 8	2+	217	107	78	40-10-20	70	
3/ 9	Trace	170	147	...	40- 0-20	60	
3/10	Trace	157	182	116	50- 0-20	60	
3/11	...	162	142	157	40- 4 every 2 hr.	56	Injection omitted at 11 p.m. and 3 a.m.
3/12	—	182	150	145	4 every 2 hr.	40	Injection omitted at 11 p.m. and 3 a.m.
3/13	Trace	281	122	78	4 every 2 hr.; 3 every 2 hr.	35	2 units every 2 hr. begun at 9 p.m.
3/14	—	192	138	186	3 every 2 hr.	30	Injection omitted at 11 p.m. and 3 a.m.
3/15	1+	231	179	167	3 every 2 hr.	36	
3/16	—	179	170	...	3 every 2 hr.	36	
3/17	—	176	162	157	3 every 2 hr.	36	
3/18	—	152	135	140	3 every 2 hr.; 2.5 every 2 hr.	33	2.5 units every 2 hr. begun at 3 p.m.
3/19	—	167	167	116	2.5 every 2 hr.	30	
3/20	—	147	90	114	2.5 every 2 hr.	30	
3/21	—	138	131	145	2.5 every 2 hr.; 2 every 2 hr.	27	2 units every 2 hr. begun at 3 p.m.
3/22	—	145	135	104	2 every 2 hr.	24	
3/23	—	145	170	105	2 every 2 hr.	24	Reaction at 3 a.m.; orange juice given
3/24	—	152	120	116	2 every 2 hr.; 2 every 3 hr.	22	2 units every 3 hr. begun at 10 p.m.
3/25	—	145	145	140	2 every 3 hr.	16	
3/26	—	162	145	142	2 every 3 hr.	16	
3/27	—	170	162	170	2 every 3 hr.	16	
3/28	—	179	150	170	2 every 3 hr.	16	
3/29	—	162	157	150	2 every 3 hr.	16	
3/30	—	173	...	147	2 every 3 hr.	16	
3/31	Trace	179	140	167	2 every 3 hr.	10	Last injection of divided doses at 4 p.m.
4/ 1	Trace	140	165	122	15- 0- 8	23	
4/ 2	Trace	204	196	147	15- 0-12	27	
4/ 3	—	131	162	66	20- 0-12	32	Reaction at 7 p.m.; orange juice given
4/ 4	..	104	...	...	20- 0- 9	29	Discharged

dosage of insulin to 3 units every two hours except at 11 p. m. and 3 a. m., making a total of 30 units. This was too great a reduction, however, for the blood sugar content rose; so the 11 p. m. and 3 a. m. injections were included, making a total dosage of 36 units a day. As the patient's tolerance improved, further reductions to 2.5 and 2 units every two hours and 2 units every three hours were made on March 18, 21 and 24, respectively. On March 30 the patient was receiving 2 units every three hours, or a total of 16 units. Injection of insulin twice daily was resumed on April 1, with doses of 15 and 8 units, which was insufficient; the proper dose was found to be 20 and 9 units, or a total of 29 units a day. On discharge the patient's diet was increased with fat to 2,450 calories.

Case 2.—H. B. (table 2), a woman aged 25, was admitted to the hospital on March 16, 1933, with severe diabetes; polyuria, polydypsia, polyphagia and glycosuria were first observed in September 1931. At that time she was placed on a carbohydrate-restricted diet. Two months later she had acidosis followed by coma, during which insulin therapy was started; she continued to take insulin until her admission to the hospital, but her home management had not been satisfactory. The physical examination gave essentially negative results.

On admission the blood sugar content was 553 mg. The patient was placed on a diet of protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm.—calories,

Table 2.—*The Values for Blood Sugar in Case 2 with Insulin in Divided Doses*

Date	Urine Sugar	Blood Sugar, Mg.	Insulin Units		Comment
			Dosage	Total	
3/16/33	4+	553	30	30	
3/17	4+	281	30-12-25	67	
3/18	...	226	40-12-25	77	
3/19	4+	281	40-15-30	85	
3/20	4+	99	40-15-25	80	Blood sugar reading taken at 2 p.m.
3/21	3+	237	37- 8 every 3 hr.	78	
3/22	1+	231	8 every 3 hr.	56	Injection omitted at 2 p.m.
3/23	—	173	8 every 3 hr.	64	
3/24	—	142	8 every 3 hr.	58	7 units injected from noon on
3/25	—	176	7 every 3 hr.	56	
3/26	1+	259	7 every 3 hr.	61	5 units added at noon
3/27	—	152	7 every 3 hr.	56	
3/28	—	204	7 every 3 hr.	56	
3/29	—	165	7 every 3 hr.	56	
3/30	—	138	7 every 3 hr.	56	
3/31	—	147	7 every 3 hr.	56	
4/ 1	—	145	7 every 3 hr.	56	
4/ 2	—	157	7 every 3 hr.	56	
4/ 3	—	105	7 every 3 hr.	56	
4/ 4	—	183	7 every 3 hr.	56	Blood sugar 107 mg. at 2 p.m., 131 mg. at 7 p.m., 37 mg. at 12 p.m., 44 mg. at 7 a.m.
4/ 5	—	167	7 every 3 hr.	56	
4/ 6	—	152	7 every 3 hr.	49	Dose omitted at 12 p.m.
4/ 7	—	109	7 every 3 hr.	49	Dose omitted at 12 p.m.
4/ 8	—	140	6 every 3 hr.	42	Dose omitted at 12 p.m.
4/ 9	—	162	6 every 3 hr.	42	Dose omitted at 12 p.m.
4/10	—	179	6 every 3 hr.	42	Dose omitted at 12 p.m.
4/11	—	138	6 every 3 hr.	42	Dose omitted at 12 p.m.
4/12	Trace	173	6 every 3 hr.	30	No injection given after 6 p.m.
4/13	2+	253	25-10-20	55	
4/14	Trace	253	30-10-25	65	Blood sugar 105 mg. at 7 p.m.
4/15	1+	217	35-10-25	70	
4/16	—	259	35- 8-27	70	Blood sugar 122 mg. at 2 p.m.
4/17	1+	306	40- 8-27	75	
4/18	..	247	40- 8-27	75	Discharged

1,887. It was necessary to increase the dosage of insulin to 40, 15 and 25 units or a total of 80 units, before the blood sugar level fell within reasonable limits, but even then the management was not satisfactory, as evidenced by appreciable glycosuria. On March 21 was instituted a regimen of divided doses with 8 units of insulin every three hours, or a total of 64 units; this produced a satisfactory decrease in blood sugar and a disappearance of sugar from the urine. On March 24 it was necessary to reduce the dosage to 7 units every three hours. On April 4 the blood sugar values obtained at intervals throughout the day and night were: 9 a. m., 183 mg.; 2 p. m., 107 mg.; 7 p. m., 131 mg.; 12 p. m., 37 mg.; 7 a. m., 44 mg., and 9 a. m., 167 mg. (meals at 7 a. m., 12 noon, and 5 p. m.). In spite of the low blood sugar value at midnight and before breakfast there were no hypo-

glycemic symptoms. However, to obviate this possibility, no injection was given at 12 p. m. from then on. With further improvement in tolerance the dosage was reduced on April 8 to 6 units every three hours except at midnight, or a total of 42 units. The patient was given this dosage until the routine of injections three times a day was resumed on April 13 with doses of 25, 10 and 20 units. This dose was insufficient and it was necessary to increase it to 40, 8 and 27, or a total of 75 units; even this dose was not entirely satisfactory, since the blood sugar value in the morning remained elevated and there was some glycosuria.

TABLE 3.—*The Values for Blood Sugar in Case 3 with Insulin in Divided Doses*

	Urine		Blood Sugar, Mg.		Insulin Units		
Date	Ketone	Sugar	9 A.M.	2 P.M.	Dosage	Total	Comment
1/26/33	—	4+	...	306	20	20	
1/27	—	1+	266	...	25-10-20	55	
1/28	—	4+	259	...	30-10-25	65	
1/29	—	3+	212	...	40-10-25	75	
1/30	—	1+	204	...	40-15-30	85	
1/31	Trace	3+	204	...	40-15-30	85	
2/ 1	—	Trace	241	...	40; 8 every 3 hr.	80	Divided dosage began at noon
2/ 2	—	—	182	...	8 every 3 hr.	64	
2/ 3	—	—	147	...	8 every 3 hr.; 7 every 3 hr.	59	
2/ 4	—	—	118	...	7 every 3 hr.; 6 every 3 hr.	51	
2/ 5	—	—	170	...	6 every 3 hr.	48	
2/ 6	—	—	167	...	6 every 3 hr.	48	
2/ 7	—	—	157	...	6 every 3 hr.	48	
2/ 8	—	—	165	...	6 every 3 hr.	48	Injection of typhoid
2/ 9	—	Trace	192	...	6 every 3 hr.	48	
2/10	—	—	211	...	6 every 3 hr.; 7 every 3 hr.	53	Infection of upper respiratory tract
2/11	—	—	159	...	7 every 3 hr.	56	
2/12	—	—	157	...	7 every 3 hr.	56	Last injection at 9 p.m.
2/13	—	--	182	...	30-8-18	56	
2/14	—	1+	...	122	30-8-18	56	
2/15	—	1+	236	104	30-5-15	50	
2/16	—	2+	230	...	35-0-22	57	
2/17	—	Trace	212	...	35-0-25	60	
2/18	Trace	2+	259	...	35-0-25	60	
2/19	Trace	Trace	...	...	35-0-30	65	
2/20	Trace	3+	192	...	35-0-30	65	
2/21	—	3+	...	...	35-0-30	65	
2/22	—	2+	189	...	35-0-35	70	
2/23	—	2+	...	...	35-0-35	70	
2/24	—	—	105	...	35-0-32	67	
2/25	..	..	...	...	35-0-32	67	Discharged

CASE 3.—LaV. L. (table 3), a youth aged 17, was admitted to the hospital on Jan. 26, 1933, with severe diabetes. He was first seen in the pediatric service over a year previously. He was discharged with instructions to follow the routine regimen, and the management of the condition was good for a time. About six months before his present admission he began to lose weight and had a recurrence of symptoms even though the dosage of insulin was increased. He was referred to the medical service for the reestablishment of his diabetic control. He was well developed and well nourished. A physical examination gave essentially negative results except for incipient bilateral cataract.

On admission the blood sugar was 306 mg. The patient was placed on a diet of protein, 70 Gm., carbohydrate, 70 Gm., and fat, 175 Gm.—calories, 2,201. Insulin in doses of 40, 15 and 30 units, or a total of 85, failed to decrease the blood sugar value taken at 9 a. m. below 200 mg. and to clear the sugar from

the urine. On February 1 he was given 8 units of insulin every three hours, or a total of 64 units. The blood sugar value promptly fell, and the sugar disappeared from the urine. On February 3 it was necessary to reduce the dose of insulin to 7 units every three hours. Management was satisfactory with this dosage until

TABLE 4.—*The Values for Blood Sugar in Case 4 with Insulin in Divided Doses*

Date	Urine		Blood Sugar, Mg.	Insulin Units		Comment
	Ketone	Sugar		Dosage	Total	
5/ 5/33	2+	3+	...	10	10	Admitted at 6 p.m.
5/ 6	2+	4+	441	10-120-20	155	Patient in coma; dextrose administered intravenously; blood sugar at 2 p.m., 200 mg.
5/ 7	2+	4+	316	24- 15-25	65	
5/ 8	Trace	3+	147	140; 8 every 3 hr.	172	Patient in coma at 5 a.m.; dextrose administered intravenously
5/ 9	Trace	—	145	8 every 3 hr.	64	
5/10	Trace	3+	124	8 every 3 hr.	56	Dose omitted at 12 p.m.
5/11	Trace	4+	231	8 every 3 hr.	64	
5/12	Trace	1+	145	8 every 3 hr.	64	
5/13	—	1+	179	8 every 3 hr.	64	
5/14	—	—	73	8 every 3 hr.	64	
5/15	—	—	...	7 every 3 hr.	56	
5/16	—	Trace	170	7 every 3 hr.	56	
5/17	—	—	82	7 every 3 hr.	56	
5/18	—	—	140	6 every 3 hr.	48	
5/19	—	—	109	6 every 3 hr.	48	Diet 75 begun at noon
5/22	—	1+	247	6 every 3 hr.	48	
5/23	—	—	90	8 every 3 hr.	64	
5/24	—	—	118	7 every 3 hr.	56	
5/26	Trace	—	140	7 every 3 hr.	56	Blood sugar 112 mg. at 2 p.m.; 129 mg. at 7 p.m.
6/ 7	—	—	142	7 every 3 hr.	56	Blood sugar 65 mg. at 2 p.m.; 36 mg. at 1 a.m.
6/ 8	—	..	129	7 every 3 hr.	56	
6/ 9	—	—	...	6 every 3 hr.	48	
6/10	—	—	87	6 every 3 hr.	48	Blood sugar 35 mg. at 6:45 a.m.; 109 mg. at 2:30 p.m.
6/11	—	—	82	6 every 3 hr.	48	Blood sugar 78 mg. at 12:20 a.m.
6/12	—	—	105	5 every 3 hr.	40	
6/13	—	—	155	4 every 3 hr.	32	
6/14	—	1+	253	4 every 3 hr.	32	
6/15	—	2+	189	4 every 3 hr.	32	
6/16	—	1+	231	4 every 3 hr.	36	4 units added at noon
6/17	—	1+	189	5 every 3 hr.	40	
6/18	—	Trace	236	5 every 3 hr.	40	
6/19	—	1+	259	5 every 3 hr.	45	5 units added at noon
6/20	—	1+	226	5 every 3 hr.	40	
6/21	Trace	1+	236	6 every 3 hr.	48	
6/22	—	—	150	6 every 3 hr.	48	
6/26	—	—	129	6 every 3 hr.	43	Blood sugar 118 mg. at 2 p.m.: 56 mg. at 12:30 a.m.
6/27	—	—	192	6 every 3 hr.	42	Last injection of divided dose given at 9 p.m.
6/28	—	1+	162	30-20	50	
6/29	Trace	4+	253	30-10-25	65	
6/30	Trace	4+	273	40- 0-30	70	Blood sugar 253 mg. at 2 p.m.
7/ 1	—	—	196	50-30	80	
7/ 2	—	—	189	50-30	80	
7/ 6	Trace	2+	241	50-10-30	90	Blood sugar 36 mg. at 2 p.m.
7/ 7	—	4+	170	50-30	80	
7/10	—	4+	159	50-30	80	Blood sugar 266 mg. at 2 p.m.
7/11	Trace	3+	162	50- 7-30	87	Blood sugar 73 mg. at 2 p.m.
7/12	—	4+	173	50- 7-30	87	Blood sugar 74 mg. at 2 p.m.; 55 mg. at 7 p.m.; 63 mg. at 4 p.m.

there developed a mild infection of the upper respiratory tract, as a result of which the blood sugar values rose; the dosage of insulin was increased to 7 units every three hours, or a total of 56 units. Regular dosage was resumed on February 13 with 30, 8 and 18 units, which was insufficient and was subsequently increased to 35 and 32, or a total of 67 units. After the return to the regular dosage, the urine showed sugar on all but the last day.

CASE 4.—E. Mc. (table 4), a youth aged 18, was admitted to the hospital on May 5, 1933. The first symptoms referable to diabetes were observed in 1927.

His first admission to the University Hospital was in 1929, at which time the diabetes was controlled with diet and insulin; he was discharged with instructions to take 20, 7 and 18 units of insulin a day. The home management of the condition was satisfactory until about a year previous to his second admission, when he had influenza. Since then the diabetes had been more severe, and he had apparently been in a state of impending coma on numerous occasions which was relieved only by food and insulin.

On admission he was placed on a diet of protein, 70 Gm., carbohydrate, 70 Gm., and fat, 175 Gm.—calories, 2,201. The patient was given 10 units of insulin before supper and before breakfast. The blood sugar content at 9 a. m. was 441 mg. Soon he showed symptoms of impending coma; a determination of carbon dioxide capacity showed an alkali reserve of 14 volumes per cent. He was immediately given 120 units of insulin and 50 Gm. of dextrose intravenously, which relieved the symptoms in a few hours. An attempt to control the diabetes on the following day with 25, 15 and 24 units of insulin failed, with a reappearance of symptoms of coma at 5 a. m. the following morning. At that time 140 units of insulin with 50 Gm. of dextrose was given, and following the relief of symptoms he was given 8 insulin units every three hours (a total of 64 units), which promptly lowered the blood sugar content and rendered the urine sugar-free, with a complete disappearance of the symptoms of acidosis. The next day because the level of the blood sugar was 124 mg. the midnight injection of 8 units was omitted. The following morning the blood sugar was 231 mg., with a 4+ reaction for sugar in the urine. Thereafter the midnight injection was included during the regimen of divided doses. Subsequently the dosage of insulin was reduced to 7, 6 and 5 and even to 4 units every three hours, but since his tolerance was not entirely stable it was occasionally necessary to increase the dosage, even after a period of satisfactory control with a lower dosage. However, for the most part, during the period of divided dosage, the blood sugar was at a reasonable level and the urine free from sugar. On May 19 the patient's diet was increased to protein, 75 Gm., carbohydrate, 75 Gm., and fat, 188 Gm.—calories, 2,358. On June 27 the patient was receiving 6 units of insulin every three hours, a total of 48 units. The next day the regular regimen was resumed, with a dosage of 30 and 20 units which was insufficient; a more satisfactory dosage was found to be 50, 7 and 30 units, or a total of 87 units, which resulted in a reasonable blood sugar value but did not keep the urine sugar-free. Blood sugar values taken at varying intervals during the day and night on several occasions were of particular interest in showing the general decrease following the ingestion of food and the low blood sugar values which obtain at night without hypoglycemic symptoms.

Case 5.—C. M. (table 5), a woman aged 66, was admitted to the hospital late in the afternoon on Feb. 20, 1932, with acute lobar pneumonia. She had moderately severe diabetes of about two and a half years' duration. The patient had previously been admitted to the hospital on Feb. 17, 1930, at which time the diabetes was first controlled. Following discharge she managed her diabetes well until the onset of the pneumonia.

On admission, the patient's blood sugar content was 253 mg.; the temperature was 103.4 F., and the respiration was rapid and somewhat labored. There was an area of dulness at the base of the right lung, the breath sounds were suppressed, and a friction rub was present. The white blood cell count was 18,400. The diagnosis of lobar pneumonia was substantiated by roentgen examination.

The patient was given a diet of protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm.—calories, 1,887; this diet was supplemented with large quantities of

fruit juice during the first few days. The patient was given 10 units of insulin on admission and 6 units at 12 p. m. and at 6 a. m. the next morning. The blood sugar content was 236 mg. at 9 a. m.; so the patient was given 12 insulin units at noon, and a dosage of 6 units every four hours was started at 4 p. m. The blood sugar level remained somewhat high, and the dosage of insulin was further increased to 7 units every three hours on the fifth day of observation, which resulted in a satisfactory blood sugar level.

The pneumonia was treated in the usual way, including the administration of oxygen by a nasal catheter and forcing of fluids. The acute symptoms rapidly subsided in three or four days, with the temperature below 101 F. On March 2 roentgen examination revealed good clearing of the pneumonic process.

TABLE 5.—*The Values for Blood Sugar in Case 5 with Insulin in Divided Doses*

Date	Urine Sugar	Blood Sugar, Mg.	Insulin Units		Comment
			Dosage	Total	
2/20/32	Trace	253	0-0-10	10	Blood sugar reading taken at 7 p.m.
2/21	Trace	236	6-6; 6 every 4 hr.	42	Blood sugar 204 mg. at 3:30 p.m.; divided doses began at noon
2/22	—	221	6 every 4 hr.; 6 every 3 hr.	48	Changed to 6 units every 3 hr. at noon
2/23	—	173	6 every 3 hr.	48	
2/24	—	236	6 every 3 hr.; 7 every 3 hr.	53	Changed to 7 units at noon
2/25	—	173	7 every 3 hr.	56	
2/26	—	150	7 every 3 hr.	56	
2/27	—	124	7 every 3 hr.; 6 every 3 hr.	51	
2/28	—	104	6 every 3 hr.; 6 every 4 hr.	42	
2/29	—	118	6 every 4 hr.; 5 every 4 hr.	32	
3/ 1	—	131	5 every 4 hr.; 10	25	Divided dosage ended at noon
3/ 2	—	79	20-0-7	27	
3/ 3	—	112	15	15	
3/ 4	—	131	15	15	
4/ 5	—	102	15	15	
3/ 6	—	105	12	12	
3/ 7	—	105	9	9	
3/ 8	—	157	7	7	
3/ 9	—	147	7	7	
3/10	—	110	7	7	
3/11	—	105	7	7	
3/12	..	182	0	0	Discharged

As the pneumonic condition improved there was a marked improvement in the diabetes, necessitating a rapid reduction in the dosage of insulin. On March 1 the patient was receiving 5 units of insulin every four hours, or a total of 30 units. The following day regular dosage was resumed with 20 and 7 units; the blood sugar value in the morning was 79 mg. The dose of insulin was reduced to 15 units before breakfast only. The rapid improvement continued with the disappearance of the pneumonia, and the patient was discharged on March 12 without further treatment with insulin.

CASE 6.—L. C. (table 6), a woman aged 22, was admitted to the hospital on Feb. 2, 1932, with severe diabetes of about five years' duration. She complained of severe pain and tenderness of the right shoulder, the right hip and the left knee. The Wassermann reaction of the blood was positive; she had had leukorrhea for over a year, but no gonococci could be demonstrated in the smears. Roent-

genologically the right hip showed definite destruction of the intra-articular cartilages suggestive of infectious arthritis.

Treatment of the arthritis consisted primarily of traction and immobilization of the legs in a cast. The patient had a septic temperature, which ranged between 99 and 102 F.; the temperature slowly dropped and remained practically normal after March 18. The patient was placed in a double leg spica cast on February 13.

TABLE 6.—*The Values for Blood Sugar in Case 6 with Insulin in Divided Doses*

Date	Urine Sugar	Blood Sugar, Mg.	Insulin Units		Comment
			Dosage	Total	
2/ 2/32	...	170	8	8	
2/ 3	4+	340	15-15-20	50	
2/ 4	...	289	30-10-20	60	
2/ 5	...	316	30-10-20	72	6 units every 3 hr. began at 9 p.m.
2/ 6	...	217	6 every 3 hr.	48	
2/ 7	...	241	6 every 3 hr.; 7 every 3 hr.	53	
2/ 8	...	155	7 every 3 hr.	56	
2/ 9	...	192	7 every 3 hr.	56	
2/10	...	179	7 every 3 hr.	56	
2/12	0	131	7 every 3 hr.	56	
2/13	0	189	7 every 3 hr.	56	Blood sugar, 212 mg. at 2 p.m.
2/14	Trace	241	7 every 3 hr.	56	
2/15	0	189	7 every 3 hr.	56	
2/16	0	129	7 every 3 hr.; 6 every 3 hr.	51	
2/18	0	96	6 every 3 hr.; 6 every 4 hr.	42	
2/20	...	120	6 every 4 hr.	36	
2/21	...	95	6 every 4 hr.; 5 every 4 hr.	33	
2/22	...	118	5 every 4 hr.; 6 every 6 hr.	27	
2/23	...	196	6 every 6 hr.	24	
2/25	...	176	6 every 6 hr.	24	
2/27	0	133	6 every 6 hr.	24	
2/29	...	165	6 every 6 hr.	24	
3/ 1	...	...	6 every 6 hr.	24	Transferred to orthopedic service
3/ 3	...	186	6 every 6 hr.	24	Blood sugar reading taken at 2 p.m.
3/ 9	...	186	6 every 6 hr.	24	Blood sugar reading taken at 2 p.m.
3/21	...	72	6 every 6 hr.	24	Blood sugar reading taken at 2 p.m.
3/23	...	...	6 every 6 hr.; 5 every 6 hr.	22	
3/30	...	204	5 every 6 hr.	20	Blood sugar reading taken at 2 p.m.
3/31	...	124	5 every 6 hr.	20	
4/11	...	84	5 every 6 hr.	20	Blood sugar reading taken at 2 p.m.
4/12	...	...	5 every 6 hr.; 4 every 6 hr.	18	
4/27	...	167	4 every 6 hr.	16	
5/10	0	...	4 every 6 hr.	16	Transferred to the medical service
5/11	0	98	10	10	
5/12	0	145	7	7	
5/13	0	145	7	7	
5/14	0	192	7	7	
5/16	0	192	7	7	Discharged, receiving 10 units

Shortly afterward a pressure sore appeared, and she was transferred to the orthopedic service for treatment. The pressure necrosis responded to treatment slowly. She had received definite relief from the cast and on its removal was able to make some motion without pain. Antisyphilitic treatment was started. She was returned to the medical service on May 10 for final control of the diabetes before discharge.

The patient had been taking about 120 units of insulin daily previous to admission to the hospital. On admission the blood sugar level was 170 mg. She was placed on a diet of protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm.—

calories, 1,887. Insulin in doses of 30, 10 and 20 units, or a total of 60 units, failed to control the diabetes, for the blood sugar remained over 300 mg. On February 5, the fourth day of observation, the patient was given a dosage of 6 insulin units every three hours, which was increased to 7 units every three hours, or a total of 56 units. With this dosage management was satisfactorily established, as evidenced by the postabsorptive blood sugar content after two hours. As the acute stage of the infection subsided, the dosage of insulin was progressively reduced to 4 units every six hours on April 12. On May 11 the regular regimen was resumed, with 10 units before breakfast only. The dose was reduced to 7 units before breakfast, but that was a little too low, and the patient was discharged on May 16 receiving 10 units a day.

CASE 7.—C. J. (table 7), a youth aged 20, was admitted to the hospital on Aug. 30, 1933. He had severe diabetes of about five years' duration and had had

TABLE 7.—*The Values for Blood Sugar in Case 7 with Insulin in Divided Doses*

Date	Urine		Blood Sugar, Mg.	Insulin Units		Comment
	Ketone	Sugar		Dosage	Total	
8/30/33	3+	4+	480	25	25	Blood sugar reading taken at 3 p.m.
8/31	Trace	4+	362	25-30-25	80	
9/ 1	Trace	4+	372	30-20; 8 every 3 hr.	74	Divided doses begun at 3 p.m.; injection omitted at 12 p.m.
9/ 2	Trace	4+	372	8 every 3 hr.; 20; 10 every 3 hr.	84	Injection omitted at 12 p.m.
9/ 3	0	2+	372	10 every 3 hr.; 25; 8 every 2 hr.	103	Injection omitted at 12 p.m.
9/ 4	0	1+	316	8 every 2 hr.; 10 every 2 hr.	100	Injection omitted at 12 p.m.
9/ 5	0	0	236	10 every 2 hr.	110	Injection omitted at 12 p.m.
9/ 6	0	0	179	10 every 2 hr.; 9 every 2 hr.	104	Injection omitted at 12 p.m.
9/ 7	0	0	273	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/ 8	0	0	186	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/10	0	0	170	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/12	0	0	155	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/14	0	0	147	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/16	0	0	60	9 every 2 hr.; 8 every 2 hr.	77	Last injection of divided doses at 6 p.m.
9/17	0	0	204	40-15-30	85	
9/18	0	0	182	40-15-30	85	
9/19	0	0	266	40-15-30	85	
9/20	0	0	204	45-12-30	87	Discharged

a number of previous admissions to the hospital. Twenty-four hours after the present admission, he was operated on, and nearly 500 cc. of purulent fluid was drained from a perinephric abscess. Staphylococcus aureus was isolated from the purulent fluid.

The patient was placed on a diet of protein, 70 Gm., carbohydrate, 70 Gm., and fat, 175 Gm.—calories, 2,201. The blood sugar level on admission was 480 mg. at 3 p. m. He was given 25 units of insulin before supper and before breakfast the following morning; the blood sugar level at 9 a. m. was 362 mg. He was operated on that afternoon, following the injection of 30 units of insulin and the ingestion of 50 Gm. of dextrose in orange juice. (It is the routine preoperative procedure to give the patient 50 Gm. of dextrose either by mouth or intravenously with about 10 extra units of insulin about two hours preceding the operation.) Postoperatively 30, 20 and 25 units of insulin failed to control the diabetes. Accordingly, a regimen of divided doses was instituted, with 8 units of insulin every three hours except at 12 p. m., a dosage which was not sufficient. The dosage was increased to 8 units every two hours except at midnight, and

finally to 10 units every two hours except at midnight. This dosage reduced the blood sugar to a reasonable value with the disappearance of sugar from the urine. In the course of two days it was necessary to reduce the dosage to 9 units every two hours except at midnight. The postoperative course was satisfactory for such an extensive lesion. On the day preceding the resumption of the regular dosage, the requirement of insulin was reduced from 99 to 88 units a day. The patient was discharged on September 20 with instructions to take 45, 12 and 30 units, or a total of 87 units; the blood sugar value was somewhat elevated, but the urine was free from sugar.

R. G. Snyder, M.S., determined the blood sugar level of the patients in the eleven experimental cases in 1929-1930.

INFLUENCE OF DI-NITROPHENOL ON CARBOHYDRATE METABOLISM

MAX WISHNOFSKY, M.D.

ARTHUR P. KANE, M.D.

EDMUND L. SHLEVIN, M.D.

AND

CHARLES S. BYRON, M.D.

BROOKLYN

It is well known that a disturbance in carbohydrate metabolism occurs in conditions in which there is an increase in heat production.

In reference to this subject Wilder [1] made the following statements:

> The exophthalmic goiter syndrome reduces the ability of the diabetic patient to utilize carbohydrate; decreases the efficiency of the unit of insulin; increases the danger of sudden onset of diabetic coma, and the control of this syndrome by the administration of iodine markedly improves the carbohydrate tolerance. . . . A mild and possibly inconspicuous or latent spark of diabetes may be fanned into flame by hyperthyroidism. . . . When thyroid is given to patients with diabetes, a marked intensification of glycosuria occurs and persists some time after the drug is discontinued. . . . An improvement in tolerance [in diabetes mellitus] has occurred within a week or ten days after thyroidectomy in almost every case. . . . Boothby and I have pointed out that the influence of heavy protein dietaries in diabetes is much like that of hyperthyroidism in that such diets stimulate the metabolism by their high specific dynamic actions and that as the metabolic rate rises the tolerance falls. Fever, as is well known, elevates the metabolic rate and simultaneously depresses sugar tolerance. . . . The action of drugs with a calorigenic influence has thus far not been studied except in the case of thyroxin and epinephrine, both of which lower tolerance. In general it appears that all those measures or conditions which stimulate the general metabolism have a depressing action on the tolerance of the diabetic patient. . . . I am aware of only one exception to this generalization, namely exercise. . . . The higher the metabolic rate the greater is the demand for insulin, even though the total amount of sugar to be utilized in a given time remains constant. The lower the metabolic rate the less the amount of insulin required to do the same work in the same time.

This study was aided by a grant from the Committee on Scientific Research of the American Medical Association.

From the Medical Service of Dr. S. R. Blatteis, Divisions of Diabetes and Metabolism, and the Department of Pathology of the Jewish Hospital, Brooklyn.

1. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Arch. Int. Med. **38**:736 (Dec.) 1926.

Fitz[2] also suggested that the unfavorable influence of hyperthyroidism may be due more to the resulting increased rate of total metabolism than to any direct effect of the thyroid gland on carbohydrate metabolism.

Fever is usually associated with infection, so that it is difficult to determine to what extent the former alone is responsible for the disturbance in carbohydrate metabolism. Walinski,[3] in studies on uncomplicated elevation of the body temperature, found a rise in the blood sugar level which could be explained by the concentration of the blood.

It has been known since the latter half of the last century that exercise improves the tolerance of the diabetic patient for carbohydrates. Allen, Stillman and Fitz [4] stressed this action. More recently Gerl and Hoffman [5] have found that exercise reduces glycemia and the requirement for insulin. This action occurs in mild and moderately severe but not in severe cases of diabetes. Lawrence [6] also observed that exercise markedly enhances the blood sugar-lowering effect of insulin and drew the distinction between mild and severe cases. Grafe and Salomon [7] and Richardson and Levine [8] found that in diabetes exercise causes a depression of the respiratory quotient indicating that proportionately fat is undergoing greater oxidation. There is, however, an absolute increase in the amount of carbohydrate oxidized. This is true for patients with mild but not for those with severe diabetes.

Di-nitrophenol causes an increase in oxidative metabolism by direct stimulation of the cell. This action occurs independently of the central nervous system or of muscular contraction and is not prevented by ergotamine or by adrenalectomy or thyroidectomy.[9] It was thought of interest, therefore, to study its influence on carbohydrate metabolism both in normal persons and in patients suffering from diabetes mellitus.

---

2. Fitz, R.: Relation of Hyperthyroidism to Diabetes, Arch. Int. Med. **27**:305 (March) 1921.

3. Walinski, F.: Ueber das Verhalten des Blutzuckers und Schweisszuckers bei künstlicher Hyperthermie, Deutsche med. Wchnschr. **58**:1475, 1932.

4. Allen, F. M.; Stillman, E., and Fitz, R.: Total Dietary Regulation in Treatment of Diabetes Mellitus, Monogr. 1, New York, Rockefeller Institute for Medical Research, 1919, p. 495.

5. Gerl, A., and Hoffman, H.: Muskelarbeit und Insulinbedarf beim Diabetes, Klin. Wchnschr. **7**:59, 1928.

6. Lawrence, R. D.: Effect of Exercise on Insulin Action in Diabetes, Brit. M. J. **1**:648, 1926.

7. Grafe, E., and Salomon, H.: Ueber den Einfluss der Muskelarbeit auf die Intensität der Zuckerverbrennung beim Diabetiker, Deutsches Arch. f. klin. Med. **139**:369, 1922.

8. Richardson, H. B., and Levine, S. F.: Exercise and Respiratory Quotient in Diabetes, J. Biol. Chem. **66**:161, 1925.

9. Tainter, M. L., and Cutting, W. C.: Febrile, Respiratory and Some Other Actions of Dinitrophenol, J. Pharmacol. & Exper. Therap. **48**:410, 1933.

METHOD OF STUDY

In normal persons the influence of di-nitrophenol on the concentration of the blood sugar was examined both during fasting and after the ingestion of dextrose. The study was performed on ten patients of whom nine suffered from trivial complaints. One patient (case 2) had juvenile hypopituitarism.

In the morning, after the patients had fasted for fourteen hours, the basal metabolism was determined with the Sanborn apparatus (indirect calorimetry by the closed method). A specimen of venous blood was then taken, and the patients

TABLE 1.—*The Concentration of Dextrose in the Blood of Normal Persons During Fasting and After the Ingestion of 100 Gm. of Dextrose Before and After the Administration of Di-nitrophenol*

	Blood Sugar*							
	During Fasting		Forty-Five Min. Post Cibum		Two Hours Post Cibum		Basal Metabolism	
Case	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol
1	93	102	150	206	121	132	+11	+28
2	87	117	88	123	104	122	− 5	+42
3	100	123	163	205	117	140	+ 5	+36
4	98	125	120	180	102	127	− 4	+34
5	114	133	176	230	178	182	− 4	+17
6	120	141	200	214	164	163	− 6	+48
7	101	120	133	168	114	136	− 5	+52
8	117	121	132	115	140	166	− 6	+24
9	99	107	135	163	117	134	+10	+95
10	98	115	163	185	121	141	− 1	+28
Means	102.7	120.4	146.0	178.8	127.8	144.5		
Difference between means†	+17.7		+32.8		+16.7			
n	9		9		9			
t	6.65		4.51		5.79			
p	<0.01		<0.01		<0.01			

* Milligrams per hundred cubic centimeters of blood.
† The sign of the difference is taken as plus when the value is greater after, and as minus when the value is greater before, the administration of di-nitrophenol.

were given 100 Gm. of dextrose in sufficient aqueous solution to constitute a total volume of 500 cc. Specimens of blood were then taken forty-five minutes and two hours after the administration of the dextrose. The sugar content of the blood was determined by the Folin-Wu method. For six days following this procedure the patients took 75 mg. of alpha-di-nitrophenol orally, three times a day after meals. No changes were made in their diets. On the seventh day, early in the morning, on an empty stomach, they took 75 mg. of alpha-di-nitrophenol. One hour later the basal metabolism and the blood sugar level, both before and after the administration of dextrose, were studied exactly as on the control day, before the administration of the alpha-di-nitrophenol.

The method of study used for diabetic patients was practically identical with that followed for the normal persons. In the interval between the tests the patients received their customary diets. Those who had been taking insulin continued to do so. Seventy-five instead of 100 Gm. of dextrose was given. The sodium salt of di-nitrophenol was given in a dose of 100 mg. three times a day after meals.

The amount of sugar in the urine was also determined. The urine was collected for exactly two hours after the ingestion of the dextrose, and its sugar content was determined by Benedict's method.

ANALYSIS OF RESULTS

Results in Normal Persons.—Table 1 shows the concentration of the blood sugar during fasting and after the administration of di-nitrophenol. On inspection it is evident that there is a significant difference, the values after the administration of di-nitrophenol being uniformly higher. The impression is confirmed when the results are analyzed statistically.[10] No attempt was made to correlate the degree of rise in the concentration of the blood sugar with the rise in basal metabolism because of the small size of the series.

There is still a controversy as to whether the blood sugar level during fasting is raised in hyperthyroidism, but in at least 60 per cent of the cases the curve for the blood sugar is elevated after the administration of dextrose. Sanger and Hun [11] ascribed the heightened curve for the blood sugar to defective storage of glycogen in the liver. Richardson, Levine and Du Bois,[12] however, produced evidence against the theory that there is any defect in glycogenesis. As mentioned, Wilder [1] attributed the hyperglycemia and the glycosuria to the elevated metab-

10. The method of analysis used was that developed by R. A. Fisher (Statistical Methods for Research Workers, ed. 3, London, Oliver and Boyd, 1930, p. 104). As an example one may consider the results for the blood sugar level during fasting. The mean difference in this instance is + 17.7, the plus sign indicating that the value is higher after the administration of di-nitrophenol. The value of t is derived as follows:

$$\frac{s^2}{n'} = \frac{1}{n'(n'-1)} \Sigma (x-\overline{x})^2 = 7.09$$

$$t = \frac{\overline{x}\sqrt{n'}}{s} = 6.65$$

If the table in Fisher's book is consulted, it is found that if n equals 9, when n equals n' —1, n' being the number of cases of the series, the highest value recorded for t is 3.250, this value for t occurring once in a hundred cases. The fact that the value for t found at the fasting level is much higher than this is decidedly significant. The same holds true for the blood sugar at the forty-five minute level (t equals 4.51) and at the two hour level (t equals 5.79). For all these values of t, p is far less than 0.01. The conventional limit of significance of p is 0.05.

11. Sanger, B. J., and Hun, E. G.: The Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Sept.) 1922.

12. Richardson, H. B.; Levine, S. Z., and Du Bois, E. F.: Storage of Glycogen in Exophthalmic Goitre, J. Biol. Chem. **67**:737, 1926.

olism. Some authors contend that thyroid extract has a toxic action on the islet tissue of the pancreas.[13]

Epinephrine causes glycogenolysis and inhibits glycogenesis in the liver and probably also in the muscles. This action is probably mediated through the sympathetic nervous system.[14]

Exercise produces an initial hyperglycemia followed by hypoglycemia if the exercise is exhausting and prolonged.[15]

Experimental work has been done by Hall and his co-workers [16] on the influence of huge doses of di-nitrophenol (from 20 to 30 mg. per kilogram of body weight) on the blood sugar level during fasting in dogs. These authors found that the level was elevated 70 mg. per hundred cubic centimeters of blood. In the liver and in skeletal muscle the glycogen content fell. Examination of the liver post mortem did not reveal any anatomic lesions; nor did studies of the hepatic function reveal any changes. They considered the rise in blood sugar concentration as an indication that glycogenolysis was occurring actively.

Our experiments show that an elevation of the blood sugar level also occurs after the ingestion of dextrose. Forty-five minutes after the ingestion of an adequate amount of dextrose the tissues are flooded with dextrose and the predominant process in the liver is glycogenesis. There is no need for active glycogenolysis. The contention of Hall and his co-workers [16] is, therefore, untenable. We are at a loss to explain the mechanism by which an increase in heat production causes an elevation in the concentration of blood sugar both during fasting and after the ingestion of dextrose. It is important to note that the rise in the blood sugar level which occurs in hyperthyroidism, hypersuprarenalism and exercise must be ascribed in part to the increase in oxidative metabolism.

Results in Patients with Diabetes Mellitus.—As discussed in the review of the literature, the prevailing opinion is that all measures,

13. Shpiner, L. B.: Increased Metabolism Only One Factor in Production and Maintenance of Hyperglycemia and Glycosuria in Experimental Hyperthyroidism, Am. J. Physiol. **92**:672, 1930.

14. Sollmann, T.: Manual of Pharmacology, ed. 4, Philadelphia, W. B. Saunders Company, 1932, p. 450.

15. Levine, S. A.; Gordon, B., and Derick, C. L.: Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, J. A. M. A. **82**:1778 (May 31) 1924. Rakestraw, N. W.: Effect of Muscular Exercise upon Certain Common Blood Constituents, J. Biol. Chem. **47**:565, 1921. Rakestraw, N. W.; Barley, C. V., and Hahn, Y. D.: Further Changes in Blood Constituents Following Strenuous Muscular Exercise, J. Biol. Chem. **56**:121, 1923. Bürger, M.: Die Wirkung der Arbeit auf den Zuckergehalt des menschlichen Blutes, Ztschr. f. d. ges. exper. Med. **5**:125, 1916.

16. Hall, V. E., et al.: Carbohydrate Metabolism, Respiration, and Circulation in Animals with Basal Metabolism Heightened by Dinitrophenol, Am. J. Physiol. **106**:432, 1933.

except exercise, which stimulate the general metabolism have a depressing action on the tolerance of the diabetic patient for carbohydrates.[17] Di-nitrophenol is an ideal substance with which to test the validity of this conception, for, in the words of Hall and his associates:[16] "Dinitrophenol is well adapted to the experimental study of the various responses of the organism to conditions of accelerated tissue metabolism."

The only work on this subject has been done by Tainter, Boyes and De Eds[18] on dogs rendered totally diabetic by pancreatectomy. The scope of their work is limited, however, for they employed only lethal doses. Their conclusions are as follows: 1. Di-nitrophenol kills pancreatectomized dogs before the usual febrile and respiratory responses to the drug are fully developed. 2. This increased toxicity is conditioned by a lack of insulin since it may be partially abrogated by adequate administration of insulin. 3. There is no significant change in the acid-base equilibrium. 4. Di-nitrophenol should be used cautiously in diabetic patients because of the possibility of increased toxicity.

As an index of the effect of di-nitrophenol on the carbohydrate tolerance in diabetes we used the following criteria: (1) its effect on the blood sugar level during fasting; (2) its effect on the concentration of the blood, and (3) the excretion of dextrose in the urine after the ingestion of 75 Gm. of dextrose.

It was also necessary to take into account the possibility that the influence of the drug might be different in mild and in severe cases, because, as has been mentioned, such a difference has been observed following exercise. Purely arbitrarily, patients for whom the blood sugar value during fasting was below 250 mg. per hundred cubic centimeters were considered as having mild or moderately severe diabetes, and those for whom the value was above this level, as having severe diabetes.

In tables 2 and 3 is shown the effect of di-nitrophenol in diabetes mellitus on (1) the concentration of dextrose in the blood during fasting and (2) the concentration of dextrose in the blood and (3) the amount of dextrose in the urine after the ingestion of 75 Gm. of dextrose. A statistical analysis failed to reveal any significance in the mean values for the blood sugar before and after the administration of di-nitrophenol. This was true regardless of the severity of the diabetes. As far as the

17. Wilder.[1] Fitz.[2] In response to a query as to the use of di-nitrophenol in diabetes mellitus, the editor of The Journal of the American Medical Association answered in part as follows: "There are even stronger reasons to oppose the use of dinitrophenol when the patient has diabetes. The tolerance in diabetes is depressed by measures of all kinds that elevate the basal metabolic rate, and this is the action of dinitrophenol" (Dinitrophenol Contraindicated in Diabetes, Queries and Minor Notes, J. A. M. A. **102**:2135 [June 23] 1934).

18. Tainter, M. L.; Boyes, J. H., and DeEds, F.: Actions of Dinitrophenol in Diabetic Dogs, Arch. internat. de pharmacodyn. et de thérap. **45**:235, 1933.

TABLE 2.—*The Influence of Di-nitrophenol in Mild and Moderately Severe Cases of Diabetes on the Concentration of Dextrose in the Blood Before and After the Ingestion of 75 Gm. of Dextrose and on the Quantity of Dextrose in the Urine After the Ingestion of 75 Gm. of Dextrose*

	Blood Sugar*						Urine Sugar†			
	During Fasting		Forty-Five Minutes Post Cibum		Two Hours Post Cibum		From 0 to 2 Hours Post Cibum		Basal Metabolism	
Case	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol
1	242	152	400	328	428	336	24.4	18.0	+25	+82
2	250	196	328	308	364	384	11.2	2.6	+ 1	+33
3	150	138	250	240	300	250	5.4	0.9	+ 5	+42
4	124	240	364	360	422	460	18.4	9.0	− 2	+38
5	176	146	256	242	231	182	4.4	1.5	+ 7	+31
6	168	228	300	352	378	374	3.2	3.4	+ 4	+49
7	234	220	356	328	...	...	19.6	16.4	+25	+62
8	238	230	410	405	374	508	1.3	1.6	+ 4	+44
9	222	202	378	300	468	428	9.0	4.8	+ 4	+61
10	98	126	224	224	264	296	0.9	0.3	0	+21
11	224	244	332	360	364	328	5.9	7.1	+36	+81
Means	193.3	192.9	327.1	313.4	359.3	354.6	9.43	5.96		
Difference between means‡	−0.4		−13.7		−4.7		−3.47			
n	10		10		9		10			
t	0.217		1.20		0.190		3.18			
p	>0.9		0.2 to 0.3		0.8 to 0.9		0.01			

* In milligrams per hundred cubic centimeters of blood.
† In grams.
‡ The sign of the difference is taken as plus when the value is greater after, and as minus when the value is greater before, the administration of di-nitrophenol.

TABLE 3.—*The Influence of Di-nitrophenol in Severe Cases of Diabetes on the Concentration of Dextrose in the Blood Before and After the Ingestion of 75 Gm. of Dextrose and on the Quantity of Dextrose in the Urine After the Ingestion of 75 Gm. of Dextrose*

	Blood Sugar*						Urine Sugar†			
	During Fasting		Forty-Five Minutes Post Cibum		Two Hours Post Cibum		From 0 to 2 Hours Post Cibum		Basal Metabolism	
Case	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol	Period of Control	After Di-nitrophenol
1	374	476	526	600	566	750	25.1	15.9	+22	+69
2	272	230	410	422	556	500	12.4	4.3	+ 6	+39
3	288	302	460	404	516	516	11.8	10.3	+20	+32
4	284	272	454	400	428	508	21.9	16.1	− 7	+19
5	283	332	400	434	385	526	16.0	4.6	+14	+25
6	252	150	428	273	440	268	11.8	4.5	+23	+44
7	340	272	536	416	680	536	14.9	12.3	− 4	+28
8	364	248	566	394	508	484	13.4	5.9	+10	+30
9	266	230	384	348	500	411	17.1	11.5	+ 1	+35
Means	302.5	279.1	462.7	410.1	508.8	499.9	16.04	9.49		
Difference between means‡	−23.4		−52.6		−8.9		−6.53			
n	8		8		8		8			
t	0.995		1.86		0.204		6.25			
p	0.3 to 0.4		0.1		0.8 to 0.9		Far < 0.01			

* In milligrams per hundred cubic centimeters of blood.
† In grams.
‡ The sign of the difference is taken as plus when the value is greater after, and as minus when the value is greater before, the administration of di-nitrophenol.

excretion of dextrose in the urine is concerned, however, a significant decrease in glycosuria was observed following the ingestion of the drug, and this was more pronounced in the severe cases. Di-nitrophenol, even in lethal doses, does not produce anatomic changes in the kidneys. Since the curves for the blood sugar before and after the administration of the drug are identical, one must conclude that an elevation of the renal threshold for dextrose is produced.

The findings in these experiments offer a direct proof that an increase in oxidative metabolism does not cause a depreciation of tolerance for carbohydrates in diabetes mellitus. The decrease in tolerance which occurs in diabetes mellitus associated with hyperthyroidism and other conditions in which the heat production is increased must be ascribed to other factors.

All the patients took di-nitrophenol for one week only. No untoward reactions were observed in the normal persons. Tainter stated that the drug should be administered cautiously to diabetic patients because severe reactions are likely to occur. That has not been our experience. Of the twenty patients who used di-nitrophenol untoward symptoms developed in only one. That patient suffered from diarrhea, and whether di-nitrophenol was the cause is conjectural.

SUMMARY AND CONCLUSIONS

In normal persons, di-nitrophenol causes a significant increase in the concentration of the blood sugar both during fasting and after the ingestion of dextrose. In the present state of our knowledge the causative mechanism cannot be determined. The elevation of the blood sugar level in hyperthyroidism, hypersuprarenalism and other conditions in which there is an augmentation in heat production must in part be attributed to the increase in oxidative metabolism.

Di-nitrophenol does not cause any significant change in the concentration of the blood sugar in diabetes mellitus, either during fasting or after the ingestion of dextrose. There is, however, a decided reduction in glycosuria after the administration of dextrose, which is to be explained on the basis of an elevation of the renal threshold for dextrose. These findings offer direct proof that an increase in oxidative metabolism does not cause a depreciation in tolerance for carbohydrates in diabetes mellitus. The decrease in tolerance which occurs in diabetes mellitus associated with hyperthyroidism and other conditions in which there is an increase in heat production must be ascribed to other factors.

The findings reported here are not to be taken as a brief for the use of di-nitrophenol. The sole purpose of this work was to study the influence of increased heat production on carbohydrate metabolism.

Dr. A. S. Wiener made the statistical analysis of the data.

Progress in Internal Medicine

INFECTIOUS DISEASES

REVIEW OF THE CURRENT LITERATURE

HOBART A. REIMANN, M.D.
MINNEAPOLIS

An enormous number of papers dealing with infectious diseases have appeared during the current year. Considerable progress has been made in the more common diseases, especially in pneumonia and influenza, and in a number of rarer diseases, such as encephalitis, tetanus and psittacosis. Many new features of academic interest have developed in the field of bacteriology, especially in regard to the classification of hemolytic streptococci and to certain of its biologic reactions and in the general field of microbic dissociation.

Pneumonia.—The rational practice of regarding pneumonia from an etiologic point of view instead of from an anatomic one has gained much ground. The terms lobar pneumonia and bronchopneumonia are no longer considered satisfactory and must be qualified by terms indicating the causative organism. Even the restricted clinico-anatomic syndrome recognized as pneumococcic lobar pneumonia has been shown to be not a single disease but a group of specific infections, each caused by a different type of pneumococcus, with many clinical and pathologic features in common. The newer ideas in regard to the etiologic classification and treatment are summarized by Finland [1] and Bullowa.[1a] Cooper's work in separating pneumococci heretofore placed in group IV into twenty-nine separate types, making in all thirty-two fixed types, has been confirmed on all sides.

An interesting study by Gautier [2] deals with pneumonia as it occurs in the tropics. The similarity in the incidence of the various types of pneumococci causing pneumonia in such widely separated places as Japan, Australia, India, Ecuador, the Transvaal and Germany is remark-

From the Department of Medicine, the University of Minnesota Hospital.

1. Finland, M.: The Use of Serum in the Treatment of Pneumonia, M. Clin. North America **18**:1093, 1935.

1a. Bullowa, J. G. M.: Pneumonia Due to Pneumococcus Type XIV (Cooper) and Its Treatment with Specific Serum, J. Clin. Investigation **14**:373 (July) 1935.

2. Gautier, R.: Tropical Pneumonia, Quart. Bull. Health Organ., League of Nations **1**:64 (March) 1932.

able. His study further confirms the constancy and world-wide distribution of the types of Pneumococcus. The general mortality rate for pneumonia of all kinds, according to statistics from world-wide sources, is also remarkably constant, averaging between 30 and 40 per cent. The most frequent types of Pneumococcus encountered in cases of pneumonia are I, II, III, VIII, VII and V in approximately that order. These six types together are responsible for about 80 per cent of the cases of pneumococcic pneumonia.[1]

According to Finland and Sutliff,[3] about one fifth of pulmonary infections due to type III and one third of those due to type VIII are to be regarded not as typical lobar pneumonia but as atypical or bronchopneumonia. Infections due to types III and VIII are less often "primary" but usually complicate illness due to other causes, such as autogenous infections. It has also been shown that occasionally several types of Pneumococcus may be encountered in the same patient;[4] in such a case (*a*) one type may be the effective invader and the other incidental, (*b*) two types may concurrently produce infection or (*c*) different types may cause consecutive infections. Finland and Winkler,[5] corroborating the results of older studies, show that recurrence of pneumonia took place in 16.5 per cent of 1,000 cases. Subsequent attacks were due to the same type or to different types of Pneumococcus. Several papers, including publications from Germany and England,[6] further attest to the value of type I antiserum when properly administered.

Cohn and Lewis[7] restudied the problem of digitalis therapy in pneumonia. They concluded that: (*a*) the drug did not influence the course of events in the disease, (*b*) in the cases considered its action is beneficial when auricular fibrillation or flutter occurs, (*c*) digitalis may precipitate the occurrence of auricular fibrillation, and (*d*) heart block occurred during pneumonia in some cases when a sufficient amount of digitalis was given to bring it about.

The use of artificial pneumothorax in the treatment of lobar pneumonia has recently attracted wide attention. Favorable results are

3. Finland, M., and Sutliff, W. D.: Infections with Pneumococcus Type III and Type VIII, Arch. Int. Med. **53**:481 (April) 1934.

4. Finland, M.: The Significance of Mixed Infections in Pneumococcic Pneumonia, J. A. M. A. **103**:1681 (Dec. 1) 1934.

5. Finland, M., and Winkler, A. W.: Recurrences in Pneumococcus Pneumonia, Am. J. M. Sc. **188**:309 (Sept.) 1934.

6. Sutliff, W. D., and Finland, M.: Type I Pneumococcic Infections with Especial Reference to Specific Serum Treatment, New England J. Med. **210**:237 (Feb. 1) 1934; The Serum Treatment of Lobar Pneumonia: A Report of the Committee of the National Research Council, Brit. M. J. **1**:241 (Feb. 10) 1934.

7. Cohn, A. E., and Lewis, W. H.: Lobar Pneumonia and Digitalis, Am. J. M. Sc. **189**:457 (April) 1935.

reported by Blake and his co-workers [8] and by Behrend and Cowper.[9] The results of Hines and Bennett [10] were not as striking; an artificial crisis was induced in 4 of 12 patients, and 4 died. The best results are said to be obtained if the lung is collapsed before the third day of illness, if no adhesions are present and if only one lung is involved. Although too few patients have as yet been treated to enable one to evaluate the method with certainty, the procedure seems to induce crisis in certain instances. It is claimed that the inflamed lung is set at rest and that pleuritic pain, if present, is abolished.

Questions occurring naturally to most observers are raised in the discussion of Blake's paper [8]: (*a*) How can a consolidated lung be collapsed? (*b*) How can the presence of fibrous adhesions be determined before introducing air? (*c*) Do not further pressure in the thorax and the collapse of the adjacent uninvolved portion of the lung dangerously increase the anoxemia already present? The replies in effect are as follows: (*a*) During the early period of consolidation the lungs are still compressible, as shown by roentgenographic studies. (*b*) The presence of adhesions can be determined after the first and second attempts to introduce air. (*c*) A deliberate attempt is made to collapse all the lobes on the side involved, and no harmful effects from the reduced amount of pulmonary tissue have as yet been observed. The method is still in the experimental stage. If it is proved safe and effective the treatment of pneumonia will be simplified, especially that of pneumonia of the type for which no specific therapy exists.

A recent paper by Avery and his associates [11] reports the effectiveness of a bacterial enzyme which specifically decomposes the polysaccharide in the capsule of Pneumococcus type III in treating experimental infections due to this type of Pneumococcus in monkeys. Reports of the clinical application of the enzyme are anticipated. Thus far no specific therapy has been developed for infection with Pneumococcus type III. The outlook for overcoming pneumonia in general is dealt with in a general review by Cole.[12]

---

8. Blake, F. G.; Howard, M. E., and Hull, W. S.: The Treatment of Lobar Pneumonia by Artificial Pneumothorax, Tr. A. Am. Physicians **49**:119, 1934.

9. Behrend, A., and Cowper, R. B. G.: Artificial Pneumothorax in the Treatment of Lobar Pneumonia, J. A. M. A. **102**:1907 (June 9) 1934.

10. Hines, L. E., and Bennett, D.: Artificial Pneumothorax in the Treatment of Acute Lobar Pneumonia, Arch. Int. Med. **55**:100 (Jan.) 1935.

11. Francis, T.; Terrell, E. E.; Dubos, R., and Avery, O. T.: Experimental Type III Pneumococcus Pneumonia in Monkeys, J. Exper. Med. **59**:641 (May) 1934.

12. Cole, R.: The Outlook for Overcoming Pneumonia, Canad. M. A. J. **30**:237, 1934.

It was at one time believed that the intact body of the pneumococcus was required to evoke specific immune bodies, but in recent years evidence has accumulated to indicate the antigenic effectiveness of various soluble derivatives. The subject is discussed by Felton, Sutliff and Steele.[13] These investigators were able to induce immunity by injecting a number of fractions derived from the pneumococcus. The immunity evoked by minute amounts of certain substances was comparable in degree to that found in the serum of convalescent patients. Certain of the fractions gave rise to a fairly high degree of heterologous immunity, in contrast with vaccines which evoke homologous immunity chiefly.

Influenza.—Highly important studies on the etiology of influenza have been prompted by the original observations of Shope, who showed that influenza in swine was incited by the combination of a form of influenza bacillus and a filtrable virus. Andrewes and his associates[14] in London succeeded in isolating a filtrable virus in cases of influenza in man which could be propagated in ferrets by nasal instillation. The virus isolated was similar immunologically to the one studied by Shope. Andrewes, Laidlaw and Smith[15] subsequently infected mice with the virus. In mice and ferrets the disease was caused by the virus alone without the presence of concomitant bacteria. Immune serum prepared by hyperimmunizing horses with tissue from infected ferrets specifically protected mice against the virus. With the facts arising from these discoveries, it will be possible to investigate the cause of the next outbreak of pandemic influenza and to determine whether it is identical with that of the so-called interpandemic or seasonal influenza. Should this be the case, the value of these contributions cannot be overestimated.

The observations of Andrewes were confirmed by Francis,[16] who studied material obtained from patients during an epidemic of influenza in Puerto Rico, and by Elkeles.[16a] Eichhorn and Pyle[17] report the interesting observation that the virus obtained by Andrewes induced

13. Felton, L. D.; Sutliff, W. D., and Steele, B. F.: Antigenic Characteristics in Man of Certain Products of Pneumococcus, J. Infect. Dis. **56**:101 (March-April) 1935.

14. Smith, W.; Andrewes, C. H., and Laidlaw, P. P.: A Virus Obtained from Influenza Patients, Lancet **2**:66 (July 8) 1933.

15. Andrewes, C. H.; Laidlaw, P. P., and Smith, W.: The Susceptibility of Mice to the Virus of Human and Swine Influenza, Lancet **2**:859 (Oct. 20) 1934.

16. Francis, T.: Transmission of Influenza by a Filterable Virus, Science **80**:457 (Nov. 16) 1934.

16a. Elkeles, G.: Etiology of Influenza, Prensa méd. argent. **22**:857 (May) 1935.

17. Eichhorn, A., and Pyle, N. J.: Observations on the Relationship of the Virus of Human Influenza and Dog Distemper, J. A. M. A. **102**:2082 (June 23) 1934.

immunity in ferrets against the virus of canine distemper. Nörr [17a] comments on the relation between influenza in man and canine distemper. Dochez, Mills and Kneeland [18] succeeded in isolating a filtrable virus from patients apparently suffering from influenza which was similar to the agent which they believed to be the causative agent of the common cold. The virus was cultivated in tissue culture and was capable of producing characteristic symptoms in both man and the chimpanzee after many months of cultivation in vitro. Kairies,[19] on the other hand, questions the rôle played by a filtrable virus and still believes that the influenza bacillus of Pfeiffer in symbiosis with the streptococcus is the cause of influenza. Gundel [20] thinks that pandemics of influenza are to be attributed more to changes of resistance in the population than to an increase of virulence of the bacteria or to mixed infection. He believes that most observers still favor the hypothesis that the influenza bacillus is the cause.

Rheumatic Fever.—The cause of rheumatic fever remains undetermined. In spite of much investigation incriminating the streptococcus, the proof of its etiologic relationship to the disease has not been established. Numerous authors have attempted to isolate a filtrable virus, but without success. Swift,[21] in discussing the subject, suggests that the frequent occurrence of nonhemolytic streptococci in the blood during the disease may be due to increased permeability of abnormal mucous membrane, permitting entrance of these bacteria. In regard to the hemolytic streptococcus, Swift cites the work of Todd, who found antistreptolysins in the blood during acute rheumatic fever, and of other investigators who demonstrated precipitins for nucleoproteins of the hemolytic streptococcus. Other observers, however, found both antistreptolysins and precipitins in other diseases as well. Recent studies by Hadfield [22] and Myers [23] and their associates show that the plasma of patients with

17a. Nörr, J.: Are There Connections Between Influenza in Human Subjects and Distemper in Dogs? München. med. Wchnschr. **82**:455 (March 21) 1935.

18. Dochez, A. R.; Mills, K. C., and Kneeland, Y.: Studies of the Etiology of Influenza, Proc. Soc. Exper. Biol. & Med. **30**:1017, 1933.

19. Kairies, A.: Die Empfänglichkeit von Iltissen und Frettchen für Influenzabacillen, Ztschr. f. Hyg. u. Infektionskr. **116**:264 (Aug.) 1934.

20. Gundel, M.: Grippeproblem, Deutsche med. Wchnschr. **60**:1575, 1934.

21. Swift, H. F.: Current Conceptions of the Nature of Rheumatic Fever, Tr. Coll. Physicians Philadelphia **2**:152 (Sept.) 1934.

22. Hadfield, G.; Magee, V., and Perry, C. B.: The Lysis of Fibrin by Streptococci, Lancet **1**:834, 1934.

23. Myers, W. K.; Keefer, C. S., and Holmes, W. F.: The Resistance to Fibrinolytic Activity of the Hemolytic Streptococcus with Special Reference to Patients with Rheumatic Fever and Rheumatoid (Atrophic) Arthritis, J. Clin. Investigation **14**:119 (Jan.) 1935.

rheumatic fever is definitely resistant to fibrinolysis by streptococci (page 408). The resistance is comparable to that found in the plasma in cases of erysipelas and other infections due to the hemolytic streptococcus. Myers suggests that this property of the plasma may be due to the streptococcic infection which often precedes rheumatic fever, without necessarily having a specific etiologic relationship to the latter condition.

In discussing allergic reactions to streptococcic nucleoproteins, especially those of the hemolytic streptococcus, Swift states that children with rheumatic fever show a much higher proportion of positive reactions than a group of normal children of similar age. He further points out that patients who have previously had rheumatic fever and contract streptococcic infection are five or six times as likely to have an attack of rheumatic fever as persons who have not had rheumatism previously who contract similar streptococcic infection. The prevention of such an infection would no doubt prevent relapses of rheumatic fever. Aschoff, on the other hand, in an address before the Medical Society of Freiburg stated that the causative agent is not to be sought in any recognized streptococcus. He does not believe that the origin of the specific nodules is an allergic reaction or that allergy plays a rôle in rheumatic fever. He is not convinced of the experimental production of specific nodules.

In another paper Swift [24] discusses the chronicity of rheumatic fever as indicated by the granulomatous nature of the typical lesions, the familial or inherited background, prolonged fever, tachycardia, recurring arthritis, subcutaneous fibroid nodules and progressive valvulitis. He also regards chronic nutritional disturbance as an important factor in the disease. This may be due to a general state of undernutrition; to a deficiency of vitamin A, as suggested by Mellanby, or to a lack of vitamin C, according to Rinehart and his associates,[25] although the addition of these vitamins to the normal diet had no effect on the progress of the disease. In a paper read at Atlantic City in May, Schultz, Sendroy and Swift reported that lack of vitamins is not important in causing rheumatic fever.

The relationship of rheumatic fever to chronic rheumatoid arthritis is still a moot point. Some investigators have claimed that the transition occasionally seen from rheumatic fever to chronic arthritis in patients indicates a relationship. It seems hazardous, however, to assume an identity of etiologic factors on this basis or on that of the histologic

24. Swift, H. F.: The Chronicity of Rheumatic Fever, New England J. Med. **211**:197 (Aug. 2) 1934.

25. Rinehart, J. F.; Connor, C. L., and Mettier, S. R.: Further Observations on the Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, J. Exper. Med. **59**:97 (Jan.) 1934.

similarity of the subcutaneous nodules observed in each disease; there seems to be no reason why the two diseases cannot attack the same person.

The studies of Von Glahn and Pappenheimer [26] do not substantiate the current idea that subacute bacterial endocarditis is the result of infection of old healed or scarred valves after rheumatic fever. Infection of the cardiac valves by nonhemolytic streptococci is due to implantation of bacteria on active or unhealed rheumatic vegetations. The authors express the belief that the continued activity of rheumatic fever is indicated by the invariable occurrence on the valves of the rheumatic verrucae which are free from bacteria, and by the presence of Aschoff bodies in the myocardium in the same percentage of cases in uncomplicated rheumatic carditis.

Chronic Infectious Arthritis.—This important disease has been the subject of extensive investigation during the past few years. At the Third Conference on Rheumatic Diseases [27] in June 1934, Steindler presented evidence that foci of infection are present in the same percentage of patients with rheumatoid (infectious) arthritis as of those with degenerative osteo-arthritis. In a high percentage of cases of each type (35 and 20 per cent, respectively) at least temporary improvement was obtained by the removal of foci of infection. Although it would seem that in scattered cases one might be convinced of the relationship of cause and effect between a definite focus of infection and subsequent arthritis, many observers, including the reviewer, are skeptical of the significance attached to the problem and believe it to be greatly exaggerated. A possibility seldom considered in this regard is that persons suffering from arthritis are often in a subnormal state, and as a result the so-called foci of infection may develop.

There seems to be agreement among most observers that two distinct forms exist—rheumatoid (atrophic) arthritis of infectious origin and hypertrophic osteo-arthritis of degenerative origin. It appears also that numerous borderline cases, or those of mixed type, exist which have led some observers to believe that both diseases may be due to the same cause (Archer [28] and others).

The controversy regarding positive or negative blood cultures in cases of chronic arthritis is still unsettled. The striking discrepancy between the reports of the investigators who recovered Streptococcus from the blood of about 50 per cent of the patients and the recent

26. Von Glahn, W. C., and Pappenheimer, A. M.: Relationship Between Rheumatic and Subacute Bacterial Endocarditis, Arch. Int. Med. **55**:173 (Feb.) 1935.

27. Third Conference on Rheumatic Diseases, J. A. M. A. **103**:1732 (Dec. 1) 1934.

28. Archer, B. H.: Chronic Nonspecific Arthritis: Etiology and Treatment with Special Reference to Vaccine Therapy, J. A. M. A. **102**:1449 (May 5) 1934.

reports of those [29] who seldom find organisms in the blood is an enigma. Myers, Keefer and Holmes [23] have shown that rheumatoid arthritis is not accompanied by an increase in the antifibrinolytic property of the plasma. This observation suggests that the disease process is not associated with or preceded by an active infection with the hemolytic streptococcus.

The use of streptococcus vaccine cannot be considered a specific treatment for rheumatoid arthritis, of course, as long as the cause of the disease is uncertain. Incidentally, there is as yet no proof of a specific beneficial effect of vaccine therapy for any infectious disease. In most of the recent reports the authors [30] minimize the value of vaccine therapy, and many investigators believe that the benefits often obtained are due to nonspecific effects of foreign protein or to other causes. Clinicians of wide experience, such as Kerr and Minot and others,[31] have emphasized the importance of regarding arthritis as a systemic disease to be treated by rest, physical and orthopedic therapy, the elimination of foci of infection, change of climate and regulation of the diet [32] as may be required in the individual case. According to Hall and Myers,[33] there is no direct relationship between dietary factors and the development of chronic arthritis. Excessive consumption of carbohydrates or an apparent vitamin and mineral deficiency has no effect on the incidence of the disease. The subject of chronic arthritis is admirably summarized in a pamphlet prepared by the American Committee for the Control of Rheumatism [34] and by Hench and his associates.[34a]

---

29. (*a*) Wainwright, C. W.: The Treatment of Chronic Rheumatoid Arthritis with Streptococcus Vaccine, J. A. M. A. **103**:1357 (Nov. 3) 1934. (*b*) Dawson, M. H., and Boots, R. H.: Recent Studies in Rheumatoid (Chronic Infectious, Atropic) Arthritis, New England J. Med. **208**:1030 (May 18) 1933. (*c*) Archer.[28] (d) Cecil.[27]

30. (*a*) Cecil, R. L.: Medical Treatment of Chronic Arthritis, J. A. M. A. **103**:1583 (Nov. 24) 1934. (*b*) Short, C. L.; Dienes, L., and Bauer, W.: Autogenous Vaccines in Rheumatoid Arthritis: A Clinical Study and Critique, Am. J. M. Sc. **187**:615 (May) 1934. (*c*) Cox, K. E., and Hill, D. F.: Chronic Arthritis, Arch. Int. Med. **54**:27 (July) 1934. (*d*) Dawson and Boots.[29b]

31. Irons, E. E.: The Treatment of Chronic Arthritis: General Principles, J. A. M. A. **103**:1579 (Nov. 24) 1934. Cecil.[30a]

32. Bauer, W.: What Should a Patient with Arthritis Eat? J. A. M. A. **104**:1 (Jan. 5) 1935.

33. Hall, F. C., and Myers, W. K.: Diet in Chronic Arthritis, Arch. Int. Med. **55**:403 (March) 1935.

34. Primer on Rheumatism. Chronic Arthritis, prepared by the American Committee for the Control of Rheumatism and the Committee on Scientific Exhibit, American Medical Association, Chicago, American Medical Association, 1934.

34a. Hench, P. S.; Bauer, W.; Fletcher, A. A.; Ghrist, D.; Hall, F., and White, P.: The Present Status of the Problem of "Rheumatism" and Arthritis, Ann. Int. Med. **8**:1315, 1495 and 1673 (April, May and June) 1935.

Tuberculosis.—In a preliminary report of important observations on tuberculosis of the lungs in patients dying from other causes; Terplan [34b] points out the impracticability of adhering to a rigid classification of the types of tuberculosis into those occurring in children and those in adults on the basis solely of observations in experiments on animals. The development of progressive tuberculosis is not, except possibly in infancy and early childhood, predominantly determined by the age of the patient. Terplan's studies show that "postprimary" infection (reinfection) may produce complex changes identical with those seen in "primary" tuberculosis (first infection). The first tuberculous infection commonly occurs during the first three decades of life. Primary focal lesions may remain entirely restricted in the lung without changes in the regional lymph nodes.

Wallgren [35] reports the results of observations on 230 children vaccinated with B C G and subjected to exposure to tuberculosis at home. In only 1 of these children did roentgenographic evidence of tuberculosis develop. The children reacted positively to tuberculin after vaccination, which Wallgren believed to be evidence of satisfactory vaccination. These results are at variance with opinions recently expressed to the effect that sensitivity to tuberculin is a liability rather than an asset. The death rate from tuberculosis among infants in Gothenburg was 3.9 per thousand in 1927, the year in which B C G vaccine was introduced. In 1933 the death rate was 0.3 per thousand. It is stated that about 1,000,000 children have thus far been vaccinated without harmful results. Numerous experimental studies [36] have shown that B C G vaccine never causes progressive lesions.

The monograph of Irvine [37] contains a brief but comprehensive discussion of B C G vaccine and an inclusive bibliography. The author shows that a certain increase of immunity is produced in man by the use of the vaccine. He points out that the incidence of tuberculosis has been decreasing steadily in all civilized countries and that in some places in which inoculation is not practiced it is even lower than in countries where B C G vaccine has been in general use, as was also recently pointed out by Boynton.[38] While this may be true, the cost of

34b. Terplan, K.: Anatomic Studies of Primary and Postprimary Pulmonary Tuberculosis in White Children and Adults, Arch. Path. **17**:723 (May) 1934.

35. Wallgren, A.: Value of Calmette Vaccination in Prevention of Tuberculosis in Childhood, J. A. M. A. **103**:1341 (Nov. 3) 1934.

36. Lurie, M.: The Fate of BCG and Associated Changes in Organs of Rabbits, J. Exper. Med. **60**:163, 1934.

37. Irvine, K. N.: The BCG Vaccine, New York, Oxford University Press, 1934.

38. Boynton, R. E.: The Declining Death Rate from Tuberculosis, J. A. M. A. **104**:1875 (May 25) 1935.

achieving this decrease has been enormous; if an effective and inexpensive vaccine could be perfected to accomplish the same result there would be a great saving in national expenditure. Only further research can determine whether B C G vaccine will meet the requirement.

Many studies concerning Löwenstein's claim as to the high incidence of bacteremia in tuberculosis and the etiologic relationship of the tubercle bacillus to a varied list of diseases have been published. Although workers in Löwenstein's laboratory and his students have reported further studies substantiating these claims, most investigators have been unable to confirm his results. The matter is dealt with thoroughly by Wilson.[39] A few of the numerous other recent publications are those of Peterson and Lederman,[40] Maier,[41] Kalbfleisch,[42] Prica and Zuk [43] and Saenz.[44] It appears that Löwenstein's medium is an excellent one for the cultivation of tubercle bacillus, and that bacteremia occurs in a small percentage of patients with tuberculosis, as would be expected. However, the incidence of bacteremia is far less than that recorded by Löwenstein, and little or no evidence is at hand to confirm his rather absurd contentions that the tubercle bacillus is the cause of chronic arthritis, rheumatic fever, schizophrenia and so forth.

Numerous studies have not confirmed the reports of Fontes, Calmette, Valtis and others regarding a filtrable stage in the so-called life cycle of the tubercle bacillus.[45] It seems that the tubercle bacillus may pass through filters of the type used by some investigators and that atypical tuberculosis results from inoculation of the filtrate (Walker [45b]).

---

39. Wilson, G. S.: Tuberculous Bacillemia, Medical Research Council, Spec. Rep. Ser. 182, London, His Majesty's Stationery Office, 1933.

40. Peterson, W. F., and Lederman, H.: The Frequency of Tubercle Bacilli Bacteremia with Loewenstein's Method, Am. Rev. Tuberc. **30**:103 (July) 1934.

41. Maier, E.: The Cultivation of Tubercle Bacilli from the Blood-Stream by Loewenstein's Method, Am. Rev. Tuberc. **30**:704 (Dec.) 1934.

42. Kalbfleisch, H. H., and Kalbfleisch, E.: Unsere Erfahrungen mit dem Tuberkelbazillenzüchtungsverfahren nach E. Löwenstein, Wien. klin. Wchnschr. **47**:939 (July 27) 1934.

43. Prica, M., and Zuk, A.: Untersuchungen über die Tuberkelbazillen Kultur nach Löwenstein, Ztschr. f. Hyg. u. Infektionskr. **116**:507 (Dec.) 1934.

44. Saenz, A.: Etudes sur la bacillémie tuberculeuse, recherches expérimentales et cliniques, Ann. Inst. Pasteur **52**:645 (June) 1934.

45. (*a*) Lange, L.: Zur Frage der Filtrierbarkeit des Tuberkelbazillus, Zentralbl. f. Bakt. **115**:542 (Abt. 1) (Dec. 6) 1934. (*b*) Walker, E. L., and Sweeney, M. A.: Microscopic Demonstration of Acid-Fast Bacilli in Tuberculous Filtrates and the Production of Tuberculous "Ultravirus" Infection in Guinea-Pigs, J. Infect. Dis. **54**:182 (March-April) 1934. (*c*) Cooper, F. B.: The Filtrability of the Acid-Fast Group, ibid. **54**:236 (March-April) 1934. (*d*) Flu, P. C.: Especially Filtrable Form of Tubercle Bacilli, Nederl. tijdschr. v. geneesk. **78**:3007 (June 30) 1934.

A report of successful isolation of the active principle of tuberculin for the purpose of the much desired standardization of the tuberculin test is made by Seibert and other investigators.[46]

The experiments of Steiner [47] failed to support the hypothesis concerning the etiologic relationship of the avian tubercle bacillus to Hodgkin's disease.

Tetanus.—The treatment of tetanus has received consideration in several papers. It is by no means a settled problem. According to Taylor,[48] the great reliance placed on tetanus antitoxin as an effective therapeutic agent is derived largely from its brilliant results in prophylaxis. Taylor points out that the undue attention devoted to the use of serum therapeutically is actually harmful, since other important features relating to treatment may be neglected. He agrees with the majority of authors who have recently expressed doubt as to the value of serum given after symptoms have appeared. He places greatest emphasis on the treatment of the local wound and advocates either complete excision or complete exposure, even if the wound is healed, in the search for possible foreign bodies. Next in importance is the control of symptoms, preferably with tribrom-ethanol or sodium amytal, and, finally, the injection of a single dose of antitoxin serum (from 3,000 to 6,000 units, intramuscularly) to neutralize any uncombined toxin which may still be in circulation. The use of tremendous doses of antitoxin seems to be unnecessary. Miller and Rogers,[49] on the other hand, recommend large doses of as high as 300,000 units, given intravenously or intramuscularly. They discuss the uselessness of intraspinal injections of antitoxin.

English investigators [50] tested the use of curare or curarine in the treatment of tetanus in man and in animals. Curare seems to lessen the continuous rigidity and to relieve the spasms.

Highly important investigations on the pathogenesis of tetanus were made by Professor Abel and his co-workers.[51] In a critical analysis of

46. Seibert, F. B.; Aronson, J. D.; Reichel, J.; Clark, L. F., and Long, E. R.: Purified Protein Derivative: A Standardized Tuberculin for Uniformity in Diagnosis and Epidemiology, Am. Rev. Tuberc. (supp.) **30**:707 (Dec.) 1934.

47. Steiner, P. F.: Hodgkin's Disease, Arch. Path. **17**:749 (June) 1934.

48. Taylor, F. W.: Study of the Treatment in Acute Tetanus, J. A. M. A. **102**: 895 (March 24) 1934.

49. Miller, R. H., and Rogers, H.: Present Status of Tetanus with Special Regard to Treatment, J. A. M. A. **104**:186 (Jan. 19) 1935.

50. Cole, L.: Tetanus Treated with Curare, Lancet **2**:475 (Sept. 1) 1934. Florey, H. W.; Harding, H. E., and Fildes, P.: Treatment of Tetanus, ibid. **2**: 1036 (Nov. 10) 1934.

51. Abel, J. J.: On Poisons and Diseases and Some Experiments with the Toxin of the Bacillus Tetani, Science **79**:121 (Feb. 9) 1934. Abel, J. J.; Evans, E. A.; Hampil, B., and Lee, F. C.: Researches on Tetanus, Bull. Johns Hopkins Hosp. **56**:84 (Feb.) 1935.

the problem he points out that the current theories regarding the transportation of toxin from the source via the nerves or their lymphatics are untenable and are the most revolutionary ever proposed in medicine. He states: "The experiments in support of these theories have been so well designed and so skillfully performed by men of the highest standing, and have appeared to be so valid and irrefutable that the unusual and exceptional mode of transport of a soluble substance has been universally accepted as an entirely satisfactory explanation of the facts of the case."

His experiments are designed to show that the toxin reaches the central nervous system only by way of the blood stream. It is unreasonable, he claims, to believe (*a*) that the toxin is transported via the axis-cylinders or the tissue spaces by "protoplasmic streaming," (*b*) that there is a continuous lymphatic system connecting the peripheral nerves with the central nervous system, and (*c*) that the toxin diffuses directly into the central nervous system. The long period of incubation frequently noted in cases of tetanus is not incompatible with the arterial transportation of the toxin, since symptoms are often delayed long after the injection of numerous other chemical toxins. A certain time elapses before symptoms occur even when tetanus toxin is injected intravenously, or several days after the site of the local lesion has been excised.

These experiments of Abel, which appear so convincing, will naturally have an important bearing on the treatment of this disease. As previously mentioned, there is already skepticism regarding the merits of the intraspinal injection of antitoxin, which these experiments, of course, indicate to be worthless. Opinions as to the uselessness of tremendous therapeutic doses of antitoxin are supported if one assumes that the bacillus lives only a short time in the lesion and produces a certain amount of toxin and no more.

Poliomyelitis.—At a symposium held in December 1934 [52] several new methods of vaccination against poliomyelitis were presented, all of which were based on similar principles. They consist for the most part of the use of the living virus treated with chemicals (formaldehyde, phenol and sodium ricinoleate) to reduce its virulence. One method consists of the immunization of monkeys with very minute doses of the living, unattenuated poliomyelitis virus mixed with the active virus of vaccinia and injected intracutaneously. There appears to be no doubt that immune, virus-neutralizing substances can be evoked in animals and in children by the use of these vaccines. The possibility that the so-called attenuated virus may revert to a virulent form or that minute doses may cause infection in susceptible persons necessitates great caution in the

52. Symposium on Poliomyelitis, Science **81**:130 (Feb. 1) 1935.

practical application of this principle. Before injection of the living virus either in minute doses or in its attenuated form is carried out on a large scale in human subjects, convincing evidence will have to be forthcoming insuring the safety of the procedure. Furthermore, the low morbidity rate of poliomyelitis renders the practicability or desirability of vaccination on a large scale questionable. There is as yet no reliable evidence that the vaccine or serum [53] is effective in influencing the disease if injected after symptoms have appeared.

Controversy exists as to whether the virus enters the body through the gastro-intestinal tract [54] or through the upper respiratory tract. Evidence of the demonstration of the virus in human feces is not convincing, but there is considerable evidence to suggest that the virus enters the upper respiratory tract and is spread by droplet infection, according to Brodie and Elvidge.[55] These investigators demonstrated the neurotropic nature of the virus in experimental poliomyelitis and showed that it travels along the fibers of the olfactory nerve to the central nervous system, where it is propagated along the nerve tracts.

Encephalitis.—Reports of studies on the St. Louis epidemic of encephalitis appear in a symposium published in *The Journal of the American Medical Association* [56] and in a monograph published by the United States Public Health Service.[57] Many new questions were raised by this outbreak, and a few have been answered. The disease differed somewhat clinically from the usual form of epidemic encephalitis, but it resembled in many respects, both clinically and pathologically, a type of encephalitis which occurred in Japan in 1924 and that observed in an isolated group of cases in Illinois in 1932. Probably the greatest advance in the knowledge of this disease was the recovery of a filtrable virus which appears to be the cause of the disease. The virus was pathogenic for mice and monkeys and could be propagated in these animals. Webster, Fite and Cox were unable to demonstrate an immunologic relationship between the virus of the disease and that of epidemic encephalitis, poliomyelitis or Japanese encephalitis.

53. Serum Therapy in Poliomyelitis, editorial, J. A. M. A. **103**:262 (July 28) 1934.

54. The Gastro-Intestinal Tract and the Autonomic Nervous System in Poliomyelitis, editorial, J. A. M. A. **103**:840 (Sept. 15) 1934.

55. Brodie, M., and Elvidge, A. R.: The Portal of Entry and Transmission of the Virus of Poliomyelitis, Science **79**:235 (March 9) 1934.

56. Symposium on Epidemic Encephalitis, J. A. M. A. **103**:726 (Sept. 8) and 822 (Sept. 15) 1934.

57. Report on the St. Louis Outbreak of Encephalitis, United States Public Health Service, Pub. Health Bull. 214, 1935, p. 1.

Because of experiments reported by Traub,[58] the conclusions of numerous investigators must be accepted with caution. Traub showed that the intracerebral injection into mice of sterile bouillon provoked symptoms of encephalitis in 60 per cent. The infectious agent was carried by apparently healthy mice and was activated by the injection of the broth. The disease was strikingly like that produced by the intracerebral injection in mice of material obtained from patients with encephalitis. The situation is reminiscent of a similar one a decade ago when McCartney and Olitsky demonstrated in stock rabbits cerebral lesions identical with those believed to have been caused by the inoculation of other rabbits with the virus of human encephalitis. On the other hand, the specific neutralization of the virus believed to be the cause of the St. Louis outbreak by the serum of patients convalescing from encephalitis strongly supports the etiologic relationship of the virus to the disease. Information regarding the mode of spread of the disease is meager, although it appeared to spread from one community to another by contagion. More than one case seldom occurred in a family. Numerous observations seem to point to the mucous membranes of the upper respiratory tract as a portal of entry. Water, milk and mosquitoes apparently played no rôle. The experiments of Webster indicate that specific neutralizing powers appear in the serum of convalescent persons and animals. Mice can be protected actively or passively. Thus far, no effective therapy has been established.

The disease must not be regarded as new. It has probably occurred unrecognized in other localities, as in New York in 1929 and elsewhere. There is every reason to believe that it will appear again. As in many other infectious diseases, such as lobar pneumonia, it is becoming increasingly clear that encephalitis is not an entity due to a single type of virus but that a multiplicity of closely related viruses give rise to diseases which clinically and pathologically may be indistinguishable, but which vary in their specific immunologic characteristics.

Rivers and Scott[58a] report the occurrence of 2 cases of meningitis caused by a filtrable virus. The virus was immunologically identical with the virus isolated by Traub from mice and with that obtained from a monkey by Armstrong and Lillie. Nevertheless, the authors are confident that their strain was actually derived from the 2 patients they studied.

---

58. Traub, E.: A Filtrable Virus Recovered from White Mice, Science **81**:298 (March 22) 1935.

58a. Rivers, T. M., and Scott, T. F. M.: Meningitis in Man Caused by a Filterable Virus, Science **81**:439 (May 3) 1935.

Cancer.—The Oliver-Sharpey lectures of Andrewes,[59] in which he pointed out indirect and circumstantial evidence in favor of the view that tumors in animals may be of virus origin, require mention in this review. It is suggested that within apparently normal cells of the human body there exists a virus capable of causing cancer. The hypothesis of the parasitic origin of cancer is by no means dead, and many of the recognized facts concerning tumors are consistent with the view that the behavior of tumor cells is essentially due to their infection by a parasitic virus. The tumor of Rous found in fowls, from which a filtrable virus is obtained, resembles a neoplastic growth in several respects: It grows into tissue by infiltration; growth is independent of the needs of the host; metastasis occurs only through the agency of cells, and apart from metastases the disease remains strictly localized. Furthermore, inclusion bodies, which are usually regarded as evidence of the presence and growth of a virus, are occasionally observed in cancerous tissue. In this case it is, however, still uncertain whether or not virus and cancer are present together. Andrewes also presented and discussed a list of virus diseases producing gradations of tissue reactions ranging from necrosis, such as is caused by the virus of foot and mouth disease, to the neoplasia of malignant epithelioma in the series of epithelial reactions, and in the series of connective tissue reactions varying from the necrosis caused by canary pox to the neoplasia of mammalian sarcoma. The gradation from a reaction to virus infection to true neoplasm is made to appear obvious. Certain features of neoplasms, however, are difficult to explain on the hypothesis of a virus origin, and attempts are made to reconcile certain discordant facts.

Andrewes' views are opposed to those of Murphy [60] and of Lewis,[60a] who do not favor the theory that spontaneous tumors are due to living organisms. Murphy does not regard the Rous virus as a true virus since (*a*) it can be purified by chemical procedures ordinarily fatal to living things, (*b*) it is not antigenic, and (*c*) it is highly resistant to inactivation by ultraviolet radiation. These objections do not seem important to Andrewes when the facts are closely scrutinized. He also believes that fowl tumors having a filtrable virus and mammalian cancer are not greatly dissimilar. Andrewes' theory on the whole does not postulate that cancer is infectious in the conventional sense, as poliomyelitis, for example. The supposition is that within apparently normal cells there may be a virus capable of causing cancer. Under certain conditions, such

59. Andrewes, C. H.: Viruses in Relation to the Aetiology of Tumours, Lancet **2**:63 (July 14) and 117 (July 21) 1934.

60. Murphy, J. B.: Experimental Approach to the Cancer Problem, Bull. Johns Hopkins Hosp. **56**:1 (Jan.) 1935.

60a. Lewis, W. H.: Normal and Malignant Cells, Science **81**:545 (June 7) 1935.

as continual irritation, the dormant virus is awakened or set free, and a neoplastic growth starts. An analogy is that of the virus of herpes simplex, which appears to reside dormant in many persons until stimulated to growth or permitted to grow by entirely unrelated causes, such as a rise of body temperature, excessive smoking and so on.

Further evidence for the possible relationship of a living virus to malignant disease is presented in a series of papers by Rous and Beard.[61] These investigators studied a disease in rabbits discovered by Shope, known as rabbit papilloma. This disease has the appearance of papilloma, and the lesions are devoid of inclusion bodies. It appears in the skin of wild rabbits and is invasive until it meets obstruction. It is easily transmitted to domestic rabbits, but the causative agent cannot be recovered in active form from these animals. When implanted internally the growths proliferate and frequently cause death. They tend to recur after excision. In a word, the growth possesses the immediate characteristics whereby tumor is recognized. On the other hand, it differs from tumors as a group in its incidence, which is that of an infectious process, and in that its cause has been demonstrated to be a filtrable virus. The authors conclude that the morphologic characteristics and behavior of the generality of tumors can no longer be taken to exclude the possibility that they are produced by extraneous living entities. Murphy [60] presents arguments to substantiate his views on the matter in another publication.

Ledingham and Gye [62] claim to have succeeded in separating the infective agent of avian tumor by centrifugation at high speed. Their description of "experiments 1 and 2," however, is not clear; it reads as though the supernatant fluid were just as effective in producing tumor as the sediment. They found enormous numbers of "elementary bodies" in the deposits and demonstrated agglutinins for these forms in the serum of tumor-bearing fowls. The particles were smaller than those of vaccinia.

Typhus.—Zinsser [63] draws attention to the fact that before 1917 typhus fever was regarded as a single entity. At least two varieties of the disease have since been recognized—the classic European and the Mexican or endemic variety (tabardillo). The question arose as to whether the form of typhus fever endemic in the northeastern part of

61. Rous, P., and Beard, J. W.: A Virus-Induced Mammalian Growth with the Characters of a Tumor (the Shope Rabbit Papilloma), J. Exper. Med. **60**:701, 723 and 741 (Dec.) 1934.

62. Ledingham, J. C. G., and Gye, W. E.: On the Nature of the Filterable Tumour-Exciting Agent in Avian Sarcomata, Lancet **1**:376 (Feb. 16) 1935.

63. Zinsser, H.: Varieties of Typhus Virus and the Epidemiology of the American Form of European Typhus Fever (Brill's Disease), Am. J. Hyg. **20**:513 (Nov.) 1934.

the United States (Brill's disease) is a third variety or is identical with one of the two forms just mentioned. Experimentation has shown that Brill's disease behaves in all respects like the European type. It was established that the interepidemic reservoir or source of infection of the endemic (Mexican or murine) variety exists in rats, from which it is transmitted to man by the flea. The interepidemic reservoir of the louse-borne European variety has never been determined. It appeared unlikely that man served this purpose since the virus is demonstrable in the blood of patients for only a short time; furthermore, lice infected with the disease die in a few weeks. With this question in mind, Zinsser studied the problem by investigating the type of person who most frequently contracts Brill's disease. He found that between 1910 and 1933 approximately 90 per cent of all cases occurred among Jews who came from southeastern Europe. About 75 per cent had been in this country for over ten years, so that it was certain that fresh infection from the European source played no rôle. No connection could be traced between the cases, and there was no instance of more than one case in a family. These facts, Zinsser suggests, point to the infected human body as the permanent residence of the virus. It appears that the cases of Brill's disease which have occurred in New York and Boston are recrudescences of typhus fever (perhaps subclinical or latent) resulting from infection acquired at an earlier period in a focus of endemic typhus in Europe. This author has published a highly entertaining and instructive book [64] on typhus fever.

These views are entirely compatible with a growing mass of evidence concerning latent infection and epidemiology. The dictum "once infected, always infected" seems applicable to certain cases of numerous other infections. It appears to be especially true regarding cases of virus disease, for example, herpes simplex. Evidence of latency and relapses in one form or another is particularly obvious in cases of malaria, tuberculosis, undulant fever and syphilis. These views naturally raise the question of the relation of the healthy carrier to epidemiology in general, and especially of the disposition and treatment of healthy carriers of typhoid and diphtheria bacilli. Is there any hope of freeing these potentially dangerous persons from their infection?

As a result of many recent observations, the interpretation of the etiology of epidemics in general has been altered considerably. The older concepts placed much emphasis on the increase in virulence of comparatively avirulent or dormant organisms to account for illness in persons singly or *en masse*. While the factor of increase of virulence, either as a result of dissociation from an avirulent to a virulent variant or of a presumed change not involving dissociation, appears to be impor-

64. Zinsser, H.: Rats, Lice and History, Boston, Little, Brown & Company, 1935.

tant in certain instances, it is apparent that the factors of far greater importance are the change in susceptibility or resistance of the host and the circumstances under which infection is transmitted from the source to the susceptible recipient. This point is especially well illustrated in Zinsser's interpretation: A person who has been infected with the virus of typhus does not become ill, owing to his high resistance. The virus, however, is able to survive in his tissues until some occurrence causes suppression of resistance and permits the dormant virus to proliferate and become invasive. Typhus is not transmitted to other persons in the absence of lice or of some other means permitting the egress of the virus from the patient. Under these circumstances Zinsser predicts that Brill's disease will become extinct spontaneously.

An excellent discussion of the underlying fundamental facts concerning parasitism and disease in general can be found in a recent monograph by Theobald Smith [65] and, in a more popular form, in Zinsser's recent book.[64] Otto [66] reviews the progress made in the study of rickettsial diseases, including tsutsugamushi disease, tropical and Malay typhus, *fièvre boutonneuse,* South African tick fever and São Paulo fever of South America. Some of these diseases appear to be closely related to typhus and others to Rocky Mountain spotted fever.

Evidence of the identity of the murine (Mexican) and the European variety is presented by Mooser, Varela and Pilz.[67] According to these observers, the epidemic European form can be made to assume the characteristics of the murine variety. They concluded that no real difference exists between the two varieties. The murine (rat) strains represent the original form, whereas the epidemic strains are modifications due to prolonged propagation in the cycle of man-louse-man.

These observations, if they can be confirmed, will be of considerable significance and will furnish one of the first examples of transformation of types. Thus far, for instance, attempts to transform one variety of Brucella or of the tubercle bacillus into another have not been successful. On the other hand, the transformation of Pneumococcus from one type to another under certain highly artificial circumstances may be regarded as a precedent.

A suggestion is made by Goodman regarding thrombo-angiitis obliterans as a possible late manifestation in cases of typhus fever. Typhus fever is known to be characterized by specific endangiitis. Goodman and

65. Smith, T.: Parasitism and Disease, Princeton, N. J., Princeton University Press, 1934.

66. Otto, R.: Flecktyphus und endemische Fleckfieber, Deutsche med. Wchnschr. **60**:1299 (Aug. 31) 1934.

67. Mooser, H.; Varela, G., and Pilz, H.: Experiments on the Conversion of Typhus Strains, J. Exper. Med. **59**:137 (Feb.) 1934.

Brodie [67a] devised a skin test employing a formaldehyde-treated preparation of Rickettsia which they claim gave positive reactions in a number of cases of thrombo-angiitis obliterans. It is of interest to add that the latter disease is fairly common in northern China where typhus exists endemically.

Gonorrhea.—A rational discussion of the immunologic aspects of the treatment of gonorrhea of the urogenital tract is presented by Pelouze.[68] Conservative views of this kind based on critical observation should tend to dampen overenthusiasm in regard to certain modes of immunotherapy. The following points were emphasized: (*a*) In the presence of disease transient immunity develops lasting from a few months to a year, which appears to be specific and is not protective against the invasion of gonococci of a different type from another source; (*b*) repeated infections with the same type of gonococcus may eventually induce a symptomless carrier stage; (*c*) under these circumstances exacerbations may occur under suitable circumstances, and (*d*) the susceptibility of the host, not the virulence of the gonococcus, determines the severity of the illness. The author believes that the use of gonococcus vaccine may do harm. He thinks that owing to the lack of knowledge of the effect of vaccines used therapeutically their employment is not warranted and that uncritical reports of striking improvement resulting from this or that method of therapy are misleading and retard scientific progress.

In the same issue of *The Journal of the American Medical Association* other papers on the treatment of gonorrhea and an abstract of the discussions are published. The confused state of therapy of this disease is illustrated by the fact that thirteen different remedies, including bacteriophage, chemotherapy and electrical treatment, are championed. The use of gonococcus filtrate is discussed in a paper by Cumming and Burhans.[69] They believe that the filtrate is of specific value in treating the disease and as a diagnostic agent, but these observations are based on uncontrolled experiments and are unconvincing.

Another enthusiastic report [70] concerns the use of fever therapy induced by placing the patient in a "fever chamber," on the assumption that the gonococcus is killed by temperature at fever levels. Any report of this nature which claims that "all of the male patients . . . were

67a. Goodman, C., and Brodie, M.: A Test for Diagnosis of Thrombo-Angiitis Obliterans, Proc. Soc. Exper. Biol. & Med. **32**:1331 (May) 1935.

68. Pelouze, P. S.: The Immunologic Aspects of Gonococcic Infection, J. A. M. A. **103**:1819 (Dec. 15) 1934.

69. Cumming, R. E., and Burhans, R. A.: Experiences with the Gonococcus Filtrate (Corbus-Ferry), J. A. M. A. **104**:181 (Jan. 19) 1935.

70. Desjardins, A. U.; Stuhler, L. G., and Popp, W. C.: Fever Therapy for Gonococcus Infections, J. A. M. A. **104**:873 (March 16) 1935.

cured" by the method employed must be regarded skeptically. The authors cite several reports of studies in which the gonococcus resisted temperatures as high as 52 C. (125.6 F.) and grew at 40 C. (104 F.), yet they state that "in gonococcus infection there is no doubt that the therapeutic efficacy of fever is absolutely a function of the degree of temperature attained," although the fever produced in their patients averaged 41.7 C. (107 F.). The fact that gonococci could no longer be cultured from the pus does not necessarily indicate their destruction by heat, nor is it certain that recovery when it occurs is due solely to the bactericidal effect of heat.

A more conservative discussion of the beneficial effects of fever therapy on gonorrheal arthritis is given by Hench, Slocumb and Popp.[70a] Parenthetically, it is not yet proved that elevation of body temperature alone, as caused by diathermy, produces the same effects on the body, other than changes in temperature, as genuine fever induced by infections or the injection of foreign protein. According to several investigators,[71] significant changes in the proteins and lipids of the blood occurred after fever due to infection but not after treatment with diathermy. The value of diathermy in the treatment of infections in general is exaggerated.

Meningococcic Meningitis.—Hoyne [72] reports good results with the use of a new meningococcus serum containing antitoxin, as developed by Ferry.[73] He advocates daily intravenous and intraspinal injections of the antitoxin. It is interesting to note that Hoyne is skeptical of the value of intraspinal therapy and, as in tetanus, believes the intravenous route to be the one of choice. According to his report, the mortality rate in a group of cases was strikingly reduced by the antitoxin as compared with the results obtained with the usual antimeningococcic serum. In 102 patients treated with antitoxin the fatality rate was 20.5 per cent.

Miller [74] reports a method whereby mice can be infected with meningococcus. The organisms are suspended in mucin and injected

70a. Hench, P. S.; Slocumb, C. H., and Popp, W. C.: Fever Therapy: Results for Gonorrheal Arthritis, Chronic Infectious (Atrophic) Arthritis and Other Forms of "Rheumatism," J. A. M. A. **104**:1779 (May 18) 1935.

71. Moen, J. K.; Medes, G., and Chalek, I.: The Relative Effects of Diathermy and Infection on the Plasma Proteins, Plasma Viscosity and Suspension Stability of the Blood in Dogs, J. Lab. & Clin. Med. **19**:571 (March) 1934. Stoesser, A. V., and McQuarrie, I.: The Influence of Acute Infection and Artificial Fever on the Plasma Lipids, Am. J. Dis. Child. **49**:658 (March) 1935.

72. Hoyne, A. L.: Meningococcic Meningitis: A New Form of Therapy, J. A. M. A. **104**:980 (March 23) 1935.

73. Ferry, N. S., and Steele, A. H.: Active Immunization with Meningococcus Toxin, J. A. M. A. **104**:983 (March 23) 1935.

74. Miller, C. P.: Experimental Meningococcus Infection in Mice, Science **78**:340 (Oct. 13) 1933; Proc. Soc. Exper. Biol. & Med. **32**:1140 (April) 1935.

intraperitoneally. The mice usually die within twenty-four hours. This discovery provides a new method for the study of meningococcic infection. Miller found that antimeningococcus serum was more effective than the new antitoxin in the prevention and treatment of experimental meningococcic infection.

Amebiasis and Amebic Dysentery.—The outbreak of amebic dysentery in Chicago in 1933 aroused widespread interest in the disease. A report of this outbreak is summarized by a number of authorities.[75] Although no entirely new discovery was made, attention is drawn to several important and often overlooked facts. Amebiasis or infestation with Endamoeba histolytica without evidence of illness is far more prevalent than is usually believed. Carriers serve as a perennial source of infection and spread the infection to other persons by contaminating food and drink. Amebic dysentery may be regarded as a manifestation of amebiasis restricted to the large intestine. The specific and the general treatment of the disease have been greatly improved in recent years by the rational use of drugs of the emetine group, organic arsenicals and derivatives of oxyquinoline and other preparations and by dietary management. Successful results from the practical use of new remedies —carbarsone and vioform—in the treatment of amebiasis are reported by Reed and Johnstone.[76] Many patients treated with these drugs remained free from infection. These investigators discovered that about 10 per cent of 1,000 prisoners were infected with E. histolytica.

Experimental studies by Faust and his collaborators are referred to in an editorial in *The Journal of the American Medical Association.*[77] These investigators found a definite relationship between certain diets and experimental amebiasis in dogs. Raw liver or liver extract and cod liver oil caused rapid improvement in infected dogs. The administration of desiccated stomach or the feeding of canned salmon caused rapid and severe exacerbation of the disease.

---

75. Craig, C. F.: The Epidemiology of Amebiasis, J. A. M. A. **103**:1061 (Oct. 6) 1934. Simon, S. K.: The Clinical Diagnosis of Amebiasis, ibid. **103**: 1063 (Oct. 6) 1934. McCoy, G. W., and Chesley, A. J.: Control of Amebic Dysentery, ibid. **103**:1145 (Oct. 13) 1934. Lynch, K. M.: Prolonged Influences and Complications of Intestinal Amebiasis, ibid. **103**:1147 (Oct. 13) 1934. Meleney, H. E.: The Pathology of Amebiasis, ibid. **103**:1213 (Oct. 20) 1934. Magath, T. B.: The Laboratory Diagnosis of Amebiasis, ibid. **103**:1218 (Oct. 20) 1934. Reed, A. C.: The Treatment of Amebiasis, ibid. **103**:1224 (Oct. 20) 1934. Craig, C. F.: Amebiasis and Amebic Dysentery, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

76. Reed, A. C., and Johnstone, H. G.: Amebiasis Among One Thousand Prisoners, Am. J. Trop. Med. **14**:181 (March) 1934.

77. Effect of Diet in Experimental Amebiasis, editorial, J. A. M. A. **104**:564 (Feb. 16) 1935.

Ulcerative Colitis.—Apropos of the claim that a specific coccus is the cause of ulcerative colitis, Torrey and Montu [78] present evidence to show that no specificity pertains to various cocci isolated from material obtained from patients with the disease.

As a result of a study of the bacteriologic features of appendicitis, Gundel and his collaborators [79] believe that appendicitis is an autogenous infection caused by enteric bacteria. The most common form is the enterococcus or the closely related anhemolytic streptococcus. After perforation or in appendical abscess the colon bacillus is the most important organism. In the cases studied there was no relation between the flora of the appendix and that of the throat to suggest that the throat serves as a focus of infection.

Bacillary Dysentery.—Epidemics of dysentery due to the Sonne and the atypical Flexner varieties of dysentery bacilli are reported by Felsen and his co-workers.[80]

Two recent studies [81] have shown that the oral administration of typhoid vaccine gives rise to agglutinins in the blood stream and presumptively provides protection against infection, although to a lesser degree than subcutaneous injections does. The oral method, if subsequently proved reliable, will be of distinct advantage, obviating the unpleasant reactions and after-effects of the vaccine when given subcutaneously.

Mumps.—Johnson and Goodpasture [82] and Rocchi [83] report successful attempts to produce mumps experimentally in animals. Johnson and Goodpasture obtained a filtrable, cytotropic virus from the saliva of 4 of 6 patients with mumps, which when inoculated into monkeys produced acute, nonsuppurative parotitis. The virus has not been found in the saliva of normal persons, and it was free from demonstrable bacteria, including spirochetes.

78. Torrey, J. C., and Montu, E.: The Cultural and Agglutinative Relationships of Intestinal Streptococci, J. Infect. Dis. **55**:340 (Nov.-Dec.) 1934.

79. Gundel, M.; Pagel, W., and Süssbrich, F.: Etiology of Appendicitis, Beitr. z. path. Anat. u. z. allg. Path. **91**:399, 1933.

80. Felsen, J., and Osofsky, M. A.: Sonne Dysentery, J. A. M. A. **103**:966 (Sept. 29) 1934. Felsen, J.; Rundlett, E. V.; Sullivan, J., and Gorenberg, H.: Atypical Flexner Dysentery, ibid. **103**:1055 (Oct. 6) 1934.

81. Hakki, A.; Arif, Y., and Ahmet, M.: Parenterale und perorale Immunisierung bei der Typhusprophylaxe, Arch. f. Schiffs- u. Tropen- Hyg. **38**:356, 1934. Ruge, H.: Untersuchungen zur Frage der Typhusschutzimpfung, Zentralbl. f. Bakt. (Abt. 1) **132**:8, 1934.

82. Johnson, C. D., and Goodpasture, E. W.: An Investigation of the Etiology of Mumps, J. Exper. Med. **59**:1 (Jan.) 1934.

83. Rocchi, F.: Etiologia della parotite epidemica: Ricerche sperimentale, Policlinico (sez. med.) **41**:223, 1934.

Whooping Cough.—Shibley [84] published further evidence for ascribing the cause of whooping cough to Hemophilus pertussis. During the past few years several attempts have been made to show that the disease is due to a filtrable virus. Shibley succeeded in transmitting a disease resembling whooping cough to an ape by inoculation with influenza bacilli free from virus. The bacilli were later recovered from the trachea and lungs of the animal.

Vaccine prepared from H. pertussis has been used by a number of investigators (Sauer and Krueger) with apparent success as a prophylactic agent. These observations further strengthen the view that the disease is caused by H. pertussis.

Yellow Fever.—A good review of studies on immunization to yellow fever and a report of original work are published by Findlay.[85] His observations confirmed the work of Sawyer, Kitchen and Lloyd (1932) in regard to the practical application of immunization to yellow fever by the simultaneous injection of the fixed neurotropic virus of yellow fever and serum of human beings immune to yellow fever. He refers to the possible danger of the method of Sellards and Laigret, who inject virus alone without the addition of immune serum. The severe reactions obtained by this method indicate that slight infection results. In addition, the actual presence of virus in the body serves as a dangerous source of supply for mosquitoes who may happen to imbibe the blood and thereby spread the infection. Findlay reports the results of the vaccination of 200 persons against yellow fever. Immune bodies were present in the serum as long as sixteen months after inoculation. Thus far none of the laboratory workers who were inoculated has contracted the disease. Prior to vaccination accidental infections were common. The development of a practical method of vaccination will render the total eradication of the disease possible. Since man is the only known reservoir of infection and since the infection is transmitted by mosquitoes the life span of which does not exceed two hundred and twenty-five days, it would seem that if immunization is successful for even as short a period as one year the disease should become extinct. The situation in this respect is analogous to that in typhus fever.

Leprosy.—An excellent discussion of the etiology of leprosy has been prepared by McKinley and his colleagues,[85a] who claim to have

84. Shibley, G. S.: Etiology of Whooping Cough, Proc. Soc. Exper. Biol. & Med. **31**:576 (Feb.) 1934.

85. Findlay, G. M.: Immunization Against Yellow Fever, Tr. Roy. Soc. Trop. Med. & Hyg. **27**:437 (March) 1934; Recent Contributions to Our Knowledge of Yellow Fever, Pub. Health Rep. **50**:360 (March 15) 1935.

85a. McKinley, E. B.: The Etiology of Leprosy, Medicine **13**:377 (Dec.) 1934.

isolated and cultivated a micro-organism obtained from lepers which is beyond much doubt Mycobacterium leprae. Although all the postulates of Koch have not been fulfilled, the authors succeeded in producing suggestive lesions in monkeys with the isolated organism.

Granulocytopenia.—Although numerous attempts have been made to show that acute agranulocytosis (neutropenia or granulopenia) may be produced experimentally in animals by the use of various bacteria, Meyer and Thewlis [86] were unable to obtain similar results. Work along these lines has been more striking in clinical experience. Zia and Forkner [87] report the common association of neutropenia with kala-azar. Agranulocytosis occurred in 4 of 26 cases studied. These observations should answer the question often raised as to whether granulocytopenia is a "new" disease. There is every reason to believe that it is not new but that it has been overlooked, unrecognized or unemphasized, at least in regard to its association with kala-azar. A recent account also appears of a patient in whom acute fatal agranulocytosis developed after two injections of typhoid vaccine. I recently observed a similar phenomenon in a woman who recovered. The patient received two subcutaneous injections of typhoid vaccine a week apart and was admitted to the hospital one day after the last injection with a count of 700 leukocytes and no granulocytes. Miller and Rhoads [88] succeeded in producing granulopenia in dogs by a special diet. These observations, together with reports of many cases occurring after the administration of various drugs, lead one to suspect strongly that the causes of the syndrome are numerous and nonspecific and that some constitutional factor or sensitivity exists to account for its occasional appearance.

Fusospirochetosis.—There is still much misunderstanding regarding Vincent's disease of the mouth. There is no convincing evidence that the spiral and fusiform organisms so commonly observed in this condition are the etiologic agents. Most critical observers regard them as saprophytes which thrive in necrotic tissue. There is only the merest circumstantial evidence that neoarsphenamine has any influence on the infection. The disease, when untreated, is self-limiting. It has been observed that persons under intensive treatment with neoarsphenamine for other conditions occasionally manifest stomatitis, the lesions of

86. Meyer, O. O., and Thewlis, E. W.: A Report of Failure to Produce Granulopenia with Bacterial Toxins, J. Clin. Investigation **13**:437 (May) 1934.

87. Zia, L., and Forkner, C. E.: The Syndrome of Acute Agranulocytosis and Its Occurrence as a Complication of Kala-Azar, Am. J. M. Sc. **188**:624 (Nov.) 1934.

88. Miller, D. R., and Rhoads, C. P.: The Experimental Production in Dogs of Acute Stomatitis, Associated with Leucopenia and a Maturation Defect of the Myeloid Element of the Bone Marrow, J. Exper. Med. **61**:173 (Feb.) 1935.

which swarm with spiral and fusiform organisms. In spite of this, neoarsphenamine is still officially recommended as the specific therapeutic agent.[89] Miller and Rhoads [88] produced ulcerative stomatitis associated with fusiform and spiral organisms, leukopenia and granulopenia in dogs by means of a restricted diet. Lillie [90] showed lesions in the myelin sheaths of the nerves supplying the oral mucous membranes, and he believes that such lesions are trophic. As a result, suitable conditions for growth are provided for the spirals and fusiform organisms. Lesions could not be produced by direct inoculation of the organisms.

Gas Gangrene.—Reeves [91] calls attention to the common practice of regarding all cases of putrefactive gangrene as instances of a single disease. He shows that about 30 per cent of the cases of this type are due to organisms other than Clostridium Welchii. Specific gas bacillus antiserum should not be wasted on the treatment of infections not due to C. Welchii. On the other hand, patients suffering from wounds contaminated with soil or street dirt should be given gas gangrene antitoxin prophylactically in addition to treatment by débridement and irrigation.

Unusual and Rare Diseases.—Place and Sutton [92] present a complete clinical study of erythema arthriticum epidemicum (Haverhill fever), a disease which they, with Willner, described in 1926. It is apparently a newly recognized clinical entity, characterized by an abrupt onset, often with chills, an exanthem and arthritis. The disease occurred as a localized epidemic and was undoubtedly spread by raw milk. The causative organism is believed to be a gram-negative bacillus. It is virulent for white mice and evokes specific agglutinins in rabbits.

Dodd and Tompkins [93] report a case of histoplasmosis. The disease was first discovered in Panama in 1906 by Darling, who was in search of a disease analogous to kala-azar on this continent. DeMonbreun [94] studied the organism recovered from the patient whose case was reported by Dodd and Tompkins and succeeded in reproducing the

89. Fantus, B.: Therapy of Fusospirochetosis (Fusospirillosis), J. A. M. A. **104**:741 (March 2) 1935.

90. Lillie, R. D.: Pathology of Experimental Black-Tongue, United States Public Health Service, Nat. Inst. Health Bull. 162 (Sept.) 1933, p. 13.

91. Reeves, J. R.: Infections by Gas-Forming Anaerobic Bacilli, J. A. M. A. **104**:326 (Feb. 16) 1935.

92. Place, E. H., and Sutton, L. E.: Erythema Arthriticum Epidemicum (Haverhill Fever), Arch. Int. Med. **54**:659 (Nov.) 1934.

93. Dodd, K., and Tompkins, E. H.: A Case of Histoplasmosis of Darling in an Infant, Am. J. Trop. Med. **14**:127 (March) 1934.

94. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's Histoplasma Capsulatum, Am. J. Trop. Med. **14**:93 (March) 1934.

disease in monkeys. While the causative organism of kala-azar and that of histoplasmosis described by Darling were regarded as a protozoan parasite, DeMonbreun proved the organism in his case to be a fungus. He suggests that the disease be renamed "cytomycosis of Darling." His observations raise the question of whether or not a relationship exists between the organism causing kala-azar and that producing histoplasmosis because of many points of similarity, and invite further study along these lines.

Twenty-four cases of epidemic pleurodynia are reported by Richter and Levine.[95] This condition appears to be an infectious disease of unknown etiology, characterized by abrupt and excruciating pain in the chest or epigastrium, fever, leukopenia and subsequent recovery. Several cases may occur in a family.

Rivers and Schwentker [96] succeeded in vaccinating monkeys against psittacosis by intramuscular inoculation with the active virus of psittacosis. Virus introduced intratracheally leads to dangerous illness, whereas virus injected by other routes is harmless and evokes immunity. The intramuscular introduction of the active virus of psittacosis in moderate amounts into human subjects was harmless and led to the development of neutralizing antibodies in the blood. These studies are of importance in respect also to vaccination against poliomyelitis, encephalitis and other infections. It is highly important to determine whether it is true in general that the route of introduction of the virus determines whether illness or subclinical infection and immunity will follow.

Tamura [97] reports the cultivation of the virus of lymphogranuloma inguinale and its transmission to the guinea-pig.

I [98] describe a case of infection with Micrococcus tetragenus, characterized by purulent arthritis, meningitis and septicemia. A review of the literature revealed that more than 170 cases of this infection have been reported, but almost without exception in the European literature. The infection is probably more common than is generally believed and is either undiagnosed or is mistaken for staphylococcic infection, which it closely resembles.

---

95. Richter, A. B., and Levine, H. D.: Epidemic Pleurodynia, J. A. M. A. **102**:898 (March 24) 1934.

96. Rivers, T. M., and Schwentker, F. F.: Vaccination of Monkeys and Laboratory Workers Against Psittacosis, J. Exper. Med. **60**:211, 1934.

97. Tamura, J. T.: Cultivation of the Virus of Lymphogranuloma Inguinale and Its Use in Therapeutic Inoculation: Preliminary Report, J. A. M. A. **103**:408 (Aug. 11) 1934.

98. Reimann, H. A.: Micrococcus Tetragenus Infection, J. Clin. Investigation **14**:311 (May) 1935.

Streptococcus.—Lancefield [99] shows that hemolytic streptococci can be differented serologically by means of the precipitin reaction into the following distinct groups: group A, strains of human origin; those of group B, bovine and dairy origin; group C, those isolated from other animals; group D, those derived from cheese, and group E, those isolated from milk. Later reports indicate the existence of group F, which probably includes the minute streptococci studied by Long and Bliss,[100] and of group G, comprising strains derived from monkeys. Griffith,[100a] already noted for his fundamental researches on the pneumococcus, has finally succeeded in classifying Streptococcus pyogenes (Streptococcus haemolyticus), included in Lancefield's group A and associated with scarlet fever, tonsillitis and septic conditions, into distinct types. Many unsuccessful attempts have previously been made, notably the painstaking study of Andrewes [101] in 1932. Andrewes confirmed Griffith's earlier work to the extent of noting that three or four forms of the types of streptococci found in scarlet fever have distinctive individuality, but he is pessimistic in regard to the eventual classification of streptococci on the basis of specific agglutination. According to Griffith, there are probably thirty types, twenty-seven of which have been classified according to cultural and serologic specificity. The method of identification is relatively simple and employs the "stained slide" technic of agglutination and the combination of several types of serums into four or five groups. If agglutination occurs in any of the groups the component serums are used separately to identify the type. The analogy to the indentification of types of Pneumococcus and to the number of different types is indeed striking.

Long and Bliss [100] report studies on the isolation of a new form of minute, amphophilic hemolytic streptococcus. It was isolated from the rhinopharynx in a variety of diseases and from that of normal persons. It will be of interest to determine eventually whether the authors actually isolated a new strain or whether the minute cocci are variant forms of the usual streptococcus.

Fibrinolysis by Streptococci.—Considerable interest has been aroused by the discovery of Tillett, Edwards and Garner [102] in regard to the

99. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571 (April) 1933.

100. Long, P. H., and Bliss, E. A.: Studies upon Minute Hemolytic Streptococci, J. Exper. Med. **60**:619 (Nov.) 1934.

100a. Griffith, F.: The Serological Classification of Streptococcus Pyogenes, J. Hyg. **34**:542 (Jan. 5) 1935.

101. Andrewes, F. W., and Christie, E. M.: The Haemolytic Streptococci: Their Grouping by Agglutination, Medical Research Council, Spec. Rep. Ser. 169, p. 1, London, His Majesty's Stationery Office, 1932.

102. Tillett, W. S.; Edwards, L. B., and Garner, R. L.: Fibrinolytic Activity of Hemolytic Streptococci, J. Clin. Investigation **13**:47 (Jan.) 1934. Tillett, W. S.: ibid. **14**:276 (March) 1935.

rapid dissolution of the fibrin clot in human blood by Str. haemolyticus of the beta type obtained from human sources. Fibrinolysis is caused by an enzyme liberated by the organisms.[102] These investigators further demonstrated the development of resistance of the plasma to fibrinolysis in 75 per cent of patients after recovery from infection due to the hemolytic streptococcus. The fibrin clot from the blood of patients who died of this infection was in no instance capable of inhibiting the fibrinolytic activity. Exacerbations frequently occur in those persons who recover from infection without the development of resistance to fibrinolysis.

These observations are of importance in the understanding of infection due to the hemolytic streptococcus. The reason for the rapid spread of infection in rabbits appeared to be explained readily on the basis of liquefaction of the clot, the presence of antifibrinogenic substances and the inhibition of inflammatory fixation as a result.[103] However, as Menkin [104] points out, the original investigations showed that the clot in the normal rabbit is resistant to dissolution by streptococci. Menkin believes that the invasive capacity is referable to the mild local effects of the organism as compared with the pronounced locally injurious action of Staphylococcus aureus. The clinical application of the fibrinolytic test is referred to in the section on rheumatic fever (page 386).

Microbic Dissociation.—In the light of recent studies, the phenomenon of microbic dissociation appears to be far more complex than the simple change from the S to the R form or from the M to the S to the R form, so intensively studied during the past decade. Baerthelin, in 1918, and other workers reported the existence of a multiplicity of variants of different organisms, and in 1932 Hoffstadt and Youmans reported the isolation of eight variant forms of a single strain of Staph. aureus. Dawson [105] demonstrated the existence of at least three variants of the pneumococcus, and Paul [106] notes the occurrence of numerous intermediate forms. Eaton [107] reports an entirely different class of pneumococcus dissociants, which are characterized by autolytic properties at 37 C. (98.6 F.). These so-called P-C variants have been recovered from patients with pneumonia. Numerous variants of the streptococcus

103. Dennis, E. W., and Berberian, D. A.: A Study on the Mechanism of Invasiveness of Streptococci, J. Exper. Med. **66**:581 (Nov.) 1934.

104. Menkin, V.: Further Studies in Mechanism of Invasiveness of Pyogenic Bacteria, Proc. Soc. Exper. Biol. & Med. **32**:162 (Oct.) 1934.

105. Dawson, M. H.: Variation in the Pneumococcus, J. Path. & Bact. **39**:323, 1934.

106. Paul, J. R.: Pneumococcus Variants, J. Bact. **28**:45 (July) 1934.

107. Eaton, M. D.: Studies on Pneumococcus Variation, J. Bact. **24**:271 (March) 1934.

have also been recently studied by Ward and Lyons.[107a] Raven [108] demonstrated three variant forms of the gonococcus, one form growing as gram-positive diplococci and another as fusiform gram-negative bacilli. Transformation from one form into another was observed. Reports of extreme examples of dissociation, that is, of transformation of cocci into bacilli and vice versa, are questioned by Holman and Carson [109] on the ground of imperfect technic. I [98] report the dissociation of Micrococcus tetragenus into more than seven variant forms, five of which were distinguished by pigment formation—pink, yellow and brown. The striking differences in colony formation provided a unique opportunity for studies of microbic dissociation.

These studies are only a few of many devoted to the subject, which is of great academic interest. The knowledge gained by the studies appears exceedingly complex, yet many preexisting misunderstandings and uncertainties are thereby explained. Attempts have been made to explain the onset of, and recovery from, infectious disease, as well as the occurrence of epidemics, on the basis of microbic dissociation, but as yet the data are inconclusive. The rôle of the phenomenon appears to be only one of many factors in the etiology of, and recovery from, infectious disease.

The subject of the relationship of vitamins and nutrition to infections has been reviewed by Wilder.[110] More data have since been collected by Clausen.[111] The conclusions he reaches should do much to dampen the ardor of enthusiasts who maintain that there is a relation of vitamins to infection. He concludes that experimental studies have not shown an increase of resistance to infection when the diet of the host has been normal, nor is there evidence to support the belief that the administration of vitamins after the onset of acute infection exercises a beneficial effect on resistance. As regards infants, there exists beyond doubt a constitutional state characterized by susceptibility to infection and loss of resistance. Many features besides diet contribute to this state.

In regard to the inheritance of resistance to bacterial infection the reader is referred to an excellent review of experimental studies by

---

107a. Ward, H. K., and Lyons, C.: Studies on the Hemolytic Streptococci of Human Origin, J. Exper. Med. **61**:515 (April) 1935.

108. Raven, C.: Dissociation of the Gonococcus, J. Infect. Dis. **55**:328 (Nov.-Dec.) 1934.

109. Holman, W. L., and Carson, A. E.: Technical Errors in Studies of Bacterial Variation, J. Infect. Dis. **56**:165 (March-April) 1935.

110. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition, Arch. Int. Med. **55**:304 (Feb.) 1935.

111. Clausen, S. W.: Nutrition and Infection, J. A. M. A. **104**:793 (March 9) 1935.

Hill.[112] It has been established that between strains of the same species differences in the mortality rate from specific infections exist which can be ascribed to variations in genetic composition. Various strains of mice differ widely in their reaction to Bacillus enteritidis, for example. On the other hand, more than fifty generations of inbreeding did not lead to complete uniformity of the litter in the reaction to infection, but the possibility of breeding a strain with fairly fixed factors of resistance or susceptibility seems reasonable.

Bacteriophage therapy,[113] allergy in regard to immunity [114] and recent advances concerning the staphylococcus [115] have been thoroughly dealt with elsewhere and need no further comment in this review. Recent advances in syphilis will be discussed in a forthcoming article.

---

112. Hill, A. B.: The Inheritance of Resistance to Bacterial Infection in Animal Species, Medical Research Council, Spec. Rep. Ser. 196, London, His Majesty's Stationery Office, 1934.

113. Eaton, M. D., and Bayne-Jones, S.: Bacteriophage Therapy, J. A. M. A. **103**:1769 (Dec. 8); 1847 (Dec. 15), and 1934 (Dec. 22) 1934.

114. Rackemann, F. M.: Allergy: A Review of Current Literature, Arch. Int. Med. **55**:141 (Jan.) 1935.

115. Holman, W. L.: Progress of Medical Science: Studies on Staphylococci, Am. J. M. Sc. **189**:436 (March) 1935.

Book Reviews

The Brain as an Organ: Its Postmortem Study and Interpretation. By Frederic Wertham, Assistant Professor of Psychiatry, New York University and Bellevue Hospital Medical College; Senior Psychiatrist, Bellevue Hospital; and Florence Wertham. Introduction by Adolf Meyer. Price, $7.50. Pp. 538, with 166 illustrations. New York: The Macmillan Company, 1934.

This volume deals with the histopathology of the nervous system, mainly the brain, and with clinical correlations, the approach throughout being made from the view that the nervous system should be treated as a functional whole, a totality that is responsive in certain defined ways to the introduction of disturbing influences. In keeping with this position, the authors stress the desirability of making more extensive surveys in histopathologic examinations of the nervous system, recognizing that the distribution of lesions ranks in importance with their kind or quality. Emphasis is placed on the fact that the variety of histopathologic processes is limited, and that the same types of lesions may arise under dissimilar pathogenetic circumstances, thus indicating the need for caution in ascribing particular clinical conditions to specifically characteristic lesions.

The brief first chapter is devoted to orientation, introducing the reader to the objective and point of view of the work. This is followed by two chapters dealing with the technic of the pathologic examination, both gross and histologic, giving a comprehensive and critical outline of procedures. Chapter VII provides a highly important discussion of "The Extent of the Normal." Four chapters are concerned with descriptive accounts of lesions, including their distribution and interpretation. The remainder of the book is made up of clinicopathologic discussions: "Correlation of Lesions with Psychopathological Phenomena"; "Comparative Histopathology"; "Some Histopathological Syndromes That May Be Associated with Mental Disorder"; "Is There a Histopathology of Schizophrenia?" and "Forensic Neurohistology." A selected bibliography contains 117 titles. Grouped together in the back of the volume are 166 excellent plates, mostly drawings reproduced by the aquatone process and photomicrographs. The book is well indexed.

Dietetics for the Clinician. Milton Arlanden Bridges. Second edition. Price, $10. Pp. 970. Philadelphia: Lea & Febiger, 1935.

The first edition of the book was reviewed for the ARCHIVES in the issue of September 1933. Certain items which were objected to then have received attention. Not noticed before but found in this reviewing are the sample menus for the ketogenic diet. These provide so much carbohydrate that they could not possibly be ketogenic.

The first edition was well received, and this amplified second edition with its extensive and valuable tables will prove to be a useful volume to have on hand for ready reference in dietetic matters.

News and Comment

TENTH INTERNATIONAL CONGRESS OF THE HISTORY OF MEDICINE

The Tenth International Congress of the History of Medicine is to be held in Madrid from September 23 to 29. An especially attractive program is offered during the meetings of the congress, and arrangements have been made by the committee in charge for various tours of especial interest. The official delegates of the United States are Dr. Henry Sigerist of Baltimore, Dr. Howard Dittrick of Cleveland and Dr. Edward B. Krumbhaar of Philadelphia.